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Synthesis of (+)-*O*-Methylthalibrine by Employing a Stereocontrolled Bischler–Napieralski Reaction and an Electrochemically Generated Diaryl Ether

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An efficient electrochemical four-step route was developed for the preparation of diaryl ether derivatives by using halogenation and dehalogenation processes in addition to electrochemical phenolic oxidation and reduction reactions. The synthesis of (+)-*O*-methylthalibrine was achieved by employing this strategy along with a stereoselective Bischler–Napieralski reaction.

Introduction

Electroorganic chemical processes that avoid the use of expensive reagents and the generation of hazardous waste materials have served as key steps in a number of synthetic routes to natural and non-natural organic targets. As part of an ongoing investigation of this area, we have developed an anodic oxidation reaction for phenols, which produces one- or two-electron oxidation products that contain the respective diaryl ether **I**[1] and spirocyclic furan **II**[2] moieties (see Figure 1). From the perspective of the electron-transfer steps that are involved, these processes mimic the oxidation reactions that take place in the biosynthesis of natural products that contain these structural units.

The results of our earlier studies, which focused on the synthesis of brominated tyrosine derivatives of marine origin as exemplified by bastadin 1 (see Figure 1),[1,2] suggest that the oxidations of phenols with halogens at the *ortho* positions proceed smoothly to provide diaryl ethers.[3] In contrast, electrochemical reactions of mono-[4a] and non-halogen[4b,4c] containing phenols undergo C–C couplings to lead to diaryl products. In the efficient oxidation reaction of phenols, the halogen substituents can be considered as auxiliaries that are introduced to promote efficient diaryl ether formation and then are cleanly removed after the oxidation process. We have demonstrated the applicability of this strategy to a general synthetic method for the preparation of diaryl ethers **I** from phenols **III** (see Scheme 1). With

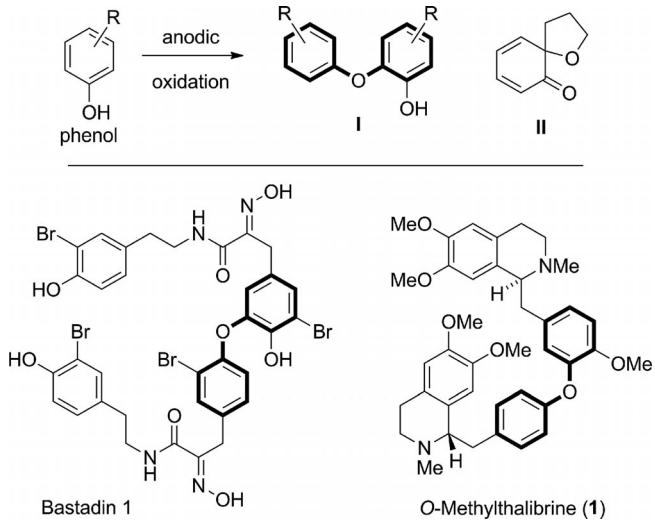

Figure 1. Oxidation reaction of phenols and natural products that contain the diaryl ether unit.

regard to synthetic methods for diaryl ethers,[1] the oxidative coupling of the same phenol species is recognized as a more economic process than other coupling reactions that use two chemical species. In this approach, halogenated phenol **IV**, which is generated from **III** (see Scheme 1, step A), is subjected to an anodic oxidation (see Scheme 1, step B) to give aryloxycyclohexadienone **VII** through radical **V** and coupling product **VI**. Next, the treatment of **VII** with Zn (see Scheme 1, step C) yields phenol **VIII**, which provides the target diaryl ether **I** upon catalytic hydrogenolysis (see Scheme 1, step D) to remove the halogen auxiliary.[5]

An example of the utility of this strategy is found in our recently described synthesis of *O*-methylthalibrine (**1**),[6] a bis(benzylisoquinoline) alkaloid that was isolated from the roots of *Thalictrum glandulosissimun*,[7a] *Thalictrum fab-*

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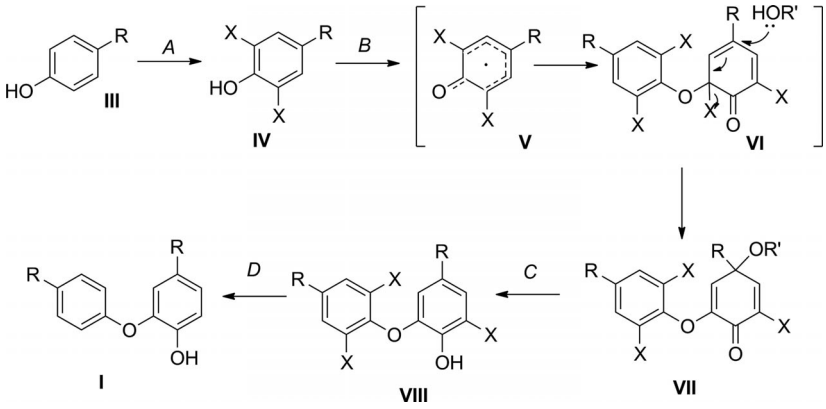


Scheme 1. Strategy for the synthesis of diaryl ethers **I** by electrochemical oxidation of halogenated phenols.

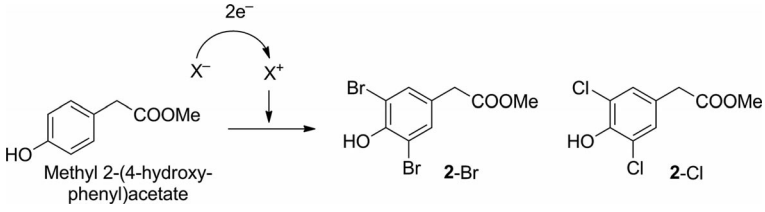
eri,[7b] and *Thalictrum minus* race B.[7c] In this developed approach, the bis(benzylisoquinoline) moiety of the target was constructed by using a Bischler–Napieralski reaction[8] of an appropriately substituted diaryl ether core, which was generated by the approach outlined in Scheme 1. The manipulation of functional groups at a late stage led to a mixture of stereoisomers that have the *O*-methylthalibrine (**1**) structure. Opatz et al.[9b] recently described the synthesis of optically active **1** by employing an Ullmann coupling reaction between two optically active benzylisoquinoline segments and relied on an α-aminonitrile alkylation[9] followed by a Noyori reduction. In the investigation described, herein, we improved the electrochemical conversion of phenols into diaryl ethers by the addition of an electrochemical halogenation (see Scheme 1, step A) and dehalogenation that was performed by using a unique flow-cell system with a Pd electrode and electrochemically generated hydrogen (see Scheme 1, step D). In this effort, we prepared an appropriately substituted diaryl ether and transformed this substance into optically active **1** by employing a diastereoselective Bischler–Napieralski reaction[8] that was mediated by (*S*)-*N*-(3,4-dimethoxyphenethyl)-1-phenylethanamine (**9**) to simultaneously install the two stereogenic centers of the target.

Results and Discussion

Electrochemical Preparation of Diaryl Ethers 4

Initial efforts focused on optimizing the halogenation of the phenols. The reactions of methyl 2-(4-hydroxyphenyl)-acetate with anodically generated Br^+ or Cl^+ ions were first explored. In a manner similar to related chemical reactions,[10] the electrochemical bromination of this substance by using the procedure described in the Experimental Section with NaBr as the bromine source led to the formation

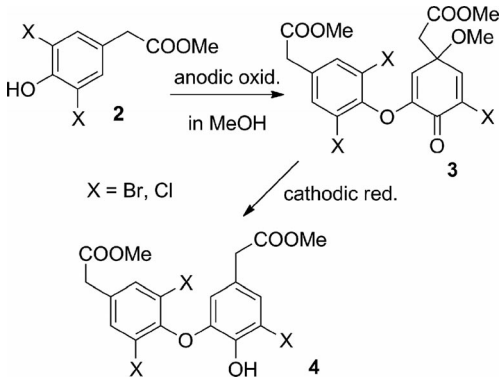
Table 1. Electrochemical halogenation of methyl 2-(4-hydroxyphenyl)acetate.



Entry	Solvent	X source (Br or Cl)	Potential [V vs. SCE]	[F/mol]	% Yield[a] of **2**-Br or **2**-Cl
1	MeOH	NaBr	0.77–0.78	4.5	86[b]
2	MeOH	NaBr	0.76	5	92[c]
3	MeOH	NaBr	0.76	5.5	97
4	MeOH	NaBr	0.88	6	86
5	MeOH	nBu$_4$NBr	0.88	5.5	87
6	MeOH	LiBr	0.83–0.85	5.5	96
7	MeOH	LiCl	1.27–1.36	5.5	14[d]
8	MeOH	nBu$_4$NCl	1.28–1.39	5.5	8[d]
9	DMF	LiCl	1.02–1.06	5.5	31
10	MeCN	nBu$_4$NCl	0.99–1.04	5.5	44
11	MeCN	nBu$_4$NCl	0.97–1.04	4	48
12	MeCN	nBu$_4$NCl	1.02–1.04	4.5	50
13	MeCN	nBu$_4$NCl	0.99	5	48

[a] Entries 1–6 for **2**-Br, Entries 7–13 for **2**-Cl. [b] Monobrominated derivative was produced in 7% yield. [c] Trace amounts of monobrominated derivative were produced. [d] Oxidation of the solvent occurred.

of 3,5-dibromo product **2**-Br in 97% (see Table 1, Entry 3). In contrast, dichloro analogue **2**-Cl was produced in 50% yield when nBu$_4$NCl was utilized as the halogen source in the corresponding anodic process (see Table 1, Entry 12). The results of a study to compare reactivities under the oxidative dimerization conditions showed that **2**-Cl was converted into the desired coupling product **3**-Cl in 60% yield, which was higher than the 35% yield that resulted from the corresponding reaction to give **3**-Br (see Scheme 2).[6] Cathodic reduction reactions of **3**-Br and **3**-Cl proceeded quantitatively to give the desired diaryl ethers **4**-Br and **4**-Cl.[6] On the basis of the described observations, **3**-Cl was selected as the substance to be used for further synthetic studies.

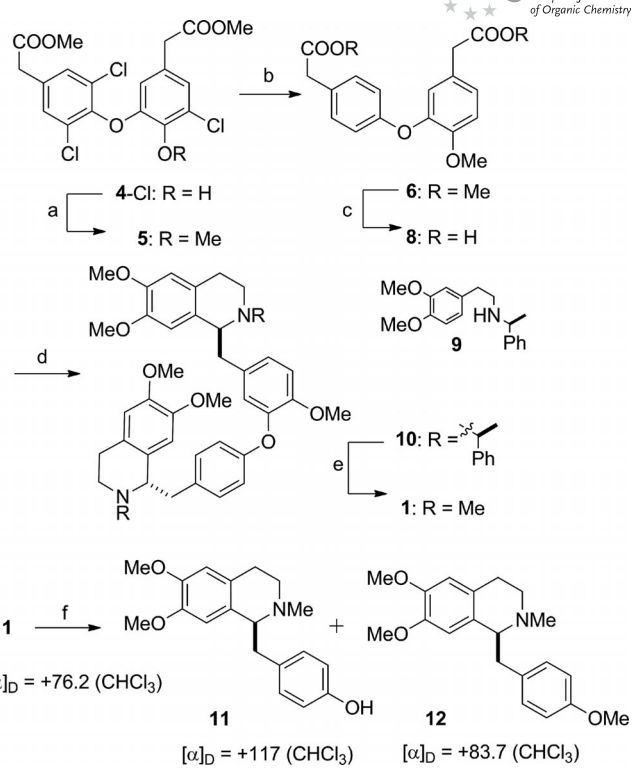


Scheme 2. Electrochemical dimerization of halogenated phenols **2** to give diaryl ethers **4** (see ref.[6]).

Pathway for the Successful Synthesis of 1

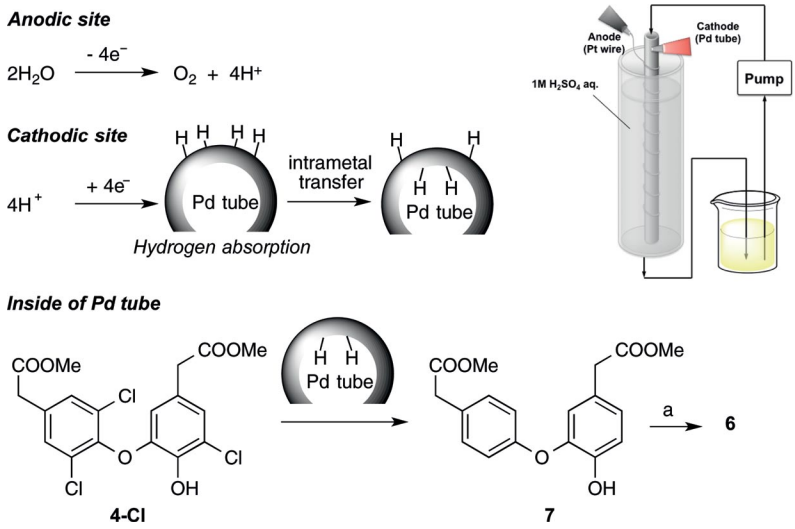
In a previous report in which the dehalogenation was carried out at a late stage to give analogues of **1** for structure–activity relationship studies, the catalytic hydrogenolysis removed only the bromo groups to give stereoisomers of **1**.[6,11] In the present approach, dehalogenation was conducted by catalytic hydrogenolysis at an early stage. Thus, after the methylation of **4**-Cl, catalytic hydrogenation of the resulting ether **5** generated **6** in 86% yield (see Scheme 3).

A reduction reaction for the dechlorination was also developed (see Scheme 4).[12] In this process, a MeOH solution that contained diaryl ether **4**-Cl was passed through a Pd tube (cathode) in a flow-cell-type system, and a Pt wire (anode) was located in aqueous H_2SO_4 outside of the system. Hydrogen, which was generated by electrolysis, was absorbed into the Pd tube and supplied through its inner surface. As a result, the successive reduction [constant current electrolysis (CCE), 62.5 mA/cm^2, 0.8 mL/min] of **4**-Cl was conducted to give **7** in 76% yield.[13] Thus, with the inclusion of this new dehalogenation reaction, the new four-step conversion of methyl 2-(4-hydroxyphenyl)acetate into the corresponding diaryl ether **7** was established by using an electrochemical procedure (see Scheme 1). Compound **7** was converted into **6** under standard methylation conditions.



Scheme 3. Synthesis of (+)-*O*-methylthalibrine (**1**) by employing diaryl ether **6**. Reagents and conditions: (a) MeI, K_2CO_3, *N*,*N*-dimethylformamide (DMF), 0 °C, 7 h, 99%; (b) H_2, 5% Pd/C, MeOH, room temp., 24 h, 86%; (c) NaOH, aqueous MeOH, room temp., 17 h, quantitative; (d) (1) **9**, (benzotriazol-1-yloxy)tris(dimethylamino)phosphonium hexafluorophosphate (BOP) reagent, Et_3N, MeCN, (2) $POCl_3$, PhMe, reflux, 16 h; (3) $NaBH_4$, MeOH, –78 °C, 6 h, 92% in two steps; (e) H_2, aqueous HCHO, Pd(OH)$_2$, room temp., 23 h, 57%; (f) Na, liquid NH_3, 2 h, **11** (26%), **12** (quantitative).

The sequence that was employed to complete the total synthesis of nonracemic **1** was initiated by the alkaline hydrolysis of **6** to produce diacid **8** (see Scheme 3). The reaction of **8** with (*S*)-*N*-(3,4-dimethoxyphenethyl)-1-phenylethanamine (**9**) provided the corresponding bis(amide) in 81% yield, which underwent a Bischler–Napieralski reaction to give **10** in 92% yield. The one-pot conversion of the chiral auxiliaries of **10** into methyl groups was carried out by using H_2, Pd(OH)$_2$, and HCHO to give the desired alkaloid **1** with an optical rotation of $[a]_D^{23}$ = +76.2 (c = 0.36, $CHCl_3$) that closely matched the reported data {ref.[7f] $[a]_D$ = +82 (c = 0.36, $CHCl_3$), ref.[9b] $[a]_D^{25}$ = +79.2 (c = 0.45, $CHCl_3$)}. To assess the selectivity of the chiral auxiliary induced Bischler-Napieralski reaction, synthetic **1** was submitted to reported Birch reduction conditions[7c] to give armepavin (**11**) with an optical rotation of $[a]_D^{20}$ = +117 (c = 1.0, $CHCl_3$) {ref.[7d] $[a]_D^{22}$ = +96 (c = 1, $CHCl_3$), ref.[9b] $[a]_D^{25}$ = +94.2 (c = 1, $CHCl_3$)} and *O*-methylarmepavine (**12**) with an optical rotation of $[a]_D^{20}$ = +83.7 (c = 0.35, $CHCl_3$) {ref.[7e] $[a]_D^{27}$ = +99 (c = 0.14, $CHCl_3$)}. The optical purities of both of these substances were determined by chiral HPLC analysis to have an (*S*)/(*R*) ratio of 93:7.



Scheme 4. Electrochemical dehalogenation of **4**-Cl. Reagents and conditions: (a) trimethylsilyldiazomethane ($TMSCHN_2$), MeOH, room temp., overnight, 90%.

Conclusions

We developed a concise route for the synthesis of optically active *O*-methylthalibrine (**1**) by employing an electrochemically prepared diaryl ether derivative. In the sequence, the two chiral centers of the target were installed simultaneously by using a stereoselective Bischler–Napieralski cyclization reaction. Finally, a reduction method was developed for the dehalogenation of chlorinated diaryl ethers. The latter process should find applications in synthetic organic chemistry.

Experimental Section

General Methods: IR spectra were recorded with a JASCO FT/IR-4200 spectrophotometer. The ^1H and ^{13}C NMR spectroscopic data were recorded with JEOL JNM-α400, JEOL JNM-AL400, and JEOL JNM-ECX400 spectrometers. High-resolution mass spectra were obtained with a Waters LCT Premier XE (ESI). Silica gel column chromatography was carried out by using Kanto Chemical Silica 60N (spherical, neutral, 63–210 μm). Preparative and analytical thin-layer chromatography (TLC) was carried out with silica gel plates (Kieselgel 60 F254, E. Merck AG, Germany). TLC was used to monitor the reactions, and the plates were visualized by using UV (254 nm) light or staining with 5% phosphomolybdic acid in ethanol as a colorizing agent followed by heating on an electric plate.

General Procedure of Electrochemical Halogenation: Electrolysis was carried out under constant current electrolysis (CCE, 10 mA/cm^2, 4–6 F/mol) conditions in an H-type cell, in which cathodic and anodic chambers were separated by an anion-exchange membrane (Neosepta AHA). A Pt plate (1 cm^2), Pt wire, and saturated calomel electrode were used as an anode, a cathode, and a reference electrode, respectively. The analyte was a solution of methyl 2-(4-hydroxyphenyl)acetate (5 mM) and the halogen source (0.1 M) in solvent, and the catholyte was a solution of the halogen source (0.1 M) and aqueous HCl (0.15 M) in solvent. The resultant mixture was concentrated in vacuo, and the residue was partitioned between EtOAc and H_2O. The organic layers were dried with Na_2SO_4 and concentrated in vacuo. The crude product was purified by chromatography.

Methyl 2-(3,5-Dibromo-4-hydroxyphenyl)acetate (2-Br): IR (film): $\tilde{\nu}$ = 2957, 1718, 1556 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.37 (s, 2 H, Ar), 5.87 (s, 1 H, ArO*H*), 3.71 (s, 3 H, CO_2CH_3), 3.49 (s, 2 H, ArCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.2 (C=O), 148.6 (Ar), 132.8 (Ar), 128.4 (Ar), 109.7 (Ar), 52.3 (CO_2CH_3), 39.4 (ArCH_2) ppm. HRMS (ESI): calcd. for $C_9H_8{}^{79}Br^{81}BrO_3$ [M + H]$^+$ 324.8853; found 324.8869.

Methyl 2-(3,5-Dichloro-4-hydroxyphenyl)acetate (2-Cl): Colorless needles (hexane/EtOAc); m.p. 88–89 °C. IR (film): $\tilde{\nu}$ = 2960, 2912, 1725, 1570 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.20 (s, 2 H, Ar), 5.84 (s, 1 H ArO*H*), 3.71 (s, 3 H, CO_2CH_3), 3.52 (s, 2 H, ArCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.1 (C=O), 146.9 (Ar), 129.0 (Ar), 127.1 (Ar), 120.9 (Ar), 52.3 (CO_2CH_3), 39.7 (ArCH_2) ppm. HRMS (ESI): calcd. for $C_9H_9{}^{35}Cl_2O_3$ [M + H]$^+$ 234.9884; found 234.9939.

Methyl 2-{3-Chloro-5-[2,6-dichloro-4-(2-methoxy-2-oxoethyl)phenoxy]-4-methoxyphenyl}acetate (5): A solution of **4**-Cl (366.4 mg, 0.845 mmol),[6] K_2CO_3 (70.0 mg, 0.507 mmol), and MeI (0.16 mL, 3.9 mmol) in DMF (8.5 mL) at 0 °C was stirred for 7 h and then diluted with aqueous HCl (2 M). The resulting mixture was extracted with $CHCl_3$. The organic layer was washed with brine, dried with Na_2SO_4, and then concentrated in vacuo. The residue was subjected to silica gel chromatography (hexane/EtOAc, 2:1) to afford **5** (375 mg, 99%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3449, 2951, 1738 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.35 (s, 2 H, Ar), 7.01 (d, J = 2 Hz, 1 H, Ar), 6.21 (d, J = 2 Hz, 1 H, Ar) 4.02 (s, 3 H, ArOCH_3), 3.76 (s, 3 H, CO_2CH_3), 3.65 (s, 3 H, CO_2CH_3), 3.63 (s, 2 H, ArCH_2), 3.43 (s, 2 H, ArCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 171.0 (C=O), 170.7 (C=O), 150.3 (Ar), 145.4 (Ar), 144.1 (Ar), 133.1 (Ar), 130.2 (Ar), 130.1 (Ar), 129.4 (Ar), 129.0 (Ar), 124.6 (Ar), 113.5 (Ar), 61.0 (ArOCH_3), 52.4 (CO_2CH_3), 52.1 (CO_2CH_3), 40.2 (ArCH_2), 39.9 (ArCH_2) ppm. HRMS (ESI): calcd. for $C_{19}H_{18}O_6{}^{35}Cl_2{}^{37}Cl$ [M + H]$^+$ 449.0134; found 449.0139.

Preparation of Methyl 2-{4-Methoxy-3-[4-(2-methoxy-2-oxoethyl)-phenoxy]phenyl}acetate (6) from Compound 5: A solution of **5** (194.3 mg, 0.434 mmol) in MeOH (4.3 mL), which contained catalytic 5% Pd/C, was stirred at room temp. under hydrogen for 24 h.

The mixture was filtered, and the filtrate was concentrated in vacuo to give a residue that was subjected to silica gel chromatography (hexane/EtOAc, 2:1) to afford **6** (129.4 mg, 0.376 mmol, 86%) as a colorless oil. IR (film): $\tilde{\nu}$ = 3001, 2952, 2840, 1735, 1609, 1585, 1507 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.19 (d, J = 8.8 Hz, 2 H, Ar), 7.03 (dd, J = 8.6, 2.2 Hz, 1 H, Ar), 6.94 (d, J = 8.6 Hz, 1 H, Ar), 6.896 (d, J = 2.2 Hz, 1 H, Ar), 6.81 (d, J = 8.8 Hz, 2 H, Ar), 3.81 (s, 3 H, ArOCH_3), 3.69 (s, 3 H, CO_2CH_3), 3.67 (s, 3 H, CO_2CH_3), 3.58 (s, 2 H, ArCH_2), 3.52 (s, 2 H, ArCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.3 (C=O), 172.1 (C=O), 157.0 (Ar), 150.6 (Ar), 147.5 (Ar), 144.8 (Ar), 130.5 (Ar), 128.1 (Ar), 126.9 (Ar), 125.6 (Ar), 122.2 (Ar), 117.3 (Ar), 112.9 (Ar), 56.2 (ArO*C*H_3), 52.1 ($CO_2C$$H_3$), 40.5 (Ar*C*$H_2$), 40.3 (Ar*C*$H_2$) ppm. HRMS (ESI): calcd. for $C_{19}H_{21}O_6$ $[M + H]^+$ 345.1338; found 345.1346.

Preparation of Methyl 2-{4-Methoxy-3-[4-(2-methoxy-2-oxoethyl)-phenoxy]phenyl}acetate (6) from Compound 7: To a solution of **7** (21.6 mg, 0.065 mmol) in MeOH (1.5 mL) was added $TMSCHN_2$ (0.33 mL, 0.196 mmol) at room temp. After stirring overnight, the mixture was concentrated in vacuo, and the residue was purified by preparative TLC (hexane/EtOAc, 1:1) to give **6** (20.3 mg, 90%).

General Procedure for the Dehalogenation: Electrolysis was carried out under the CCE conditions in a flow-cell apparatus as shown in Scheme 4. A Pd tube (3.0 × 0.2 × 100 mm, purity = 99.95%) and Pt wire were used as the cathode and anode, respectively, and were immersed in a vessel that contained an aqueous solution of H_2SO_4 (1 M). During the electrolysis at a constant current (62.5 mA/cm^2), a solution of **4**-Cl (1 mM) in MeOH was passed through the Pd tube at a rate of 0.8 min/mL. The eluent was concentrated in vacuo, and the crude product was purified by chromatography.

Methyl 2-{4-Hydroxy-3-[4-(2-methoxy-2-oxoethyl)phenoxy]phenyl}-acetate (7): IR (film): $\tilde{\nu}$ = 3005, 2954, 2843, 1733, 1597, 1507 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 7.18 (d, J = 8.7 Hz, 2 H, Ar), 6.92–6.81 (m, 5 H, Ar), 3.64 (s, 3 H, CO_2CH_3), 3.63 (s, 3 H, CO_2CH_3), 3.58 (s, 2 H, ArCH_2), 3.49 (s, 2 H, ArCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 172.1 (C=O), 155.9 (Ar), 146.6 (Ar), 143.3 (Ar), 130.9 (Ar), 129.3 (Ar), 126.4 (Ar), 125.7 (Ar), 119.9 (Ar), 118.2 (Ar), 116.3 (Ar), 52.2 ($CO_2C$$H_3$), 52.1 ($CO_2C$$H_3$), 40.4 (Ar*C*$H_2$), 40.4 (Ar*C*$H_2$) ppm. HRMS (ESI): calcd. for $C_{18}H_{18}O_6Na$ $[M + Na]^+$ 353.1001; found 353.1002.

2-{4-[5-(Carboxymethyl)-2-methoxyphenoxy]phenyl}acetic Acid (8): To a solution of **6** (101.1 mg, 0.294 mmol) in MeOH (2.2 mL) and H_2O (0.7 mL), was added aqueous NaOH (3 M, 1.0 mL) at 0 °C. After stirring for 17 h, the reaction mixture was quenched by the addition of aqueous HCl (2 M) at 0 °C, and the resulting solution was extracted with $CHCl_3$. The organic layer was washed with brine and dried with Na_2SO_4. The filtrate was concentrated in vacuo to afford **8** (94.5 mg, quantitative) as a white solid. IR (film): $\tilde{\nu}$ = 2957, 2925, 2851, 1714, 1606, 1507 cm^{-1}. ^1H NMR (400 MHz, CD_3OD): δ = 7.19 (d, J = 8.5 Hz, 2 H, Ar), 7.08 (dd, J = 1.5, 8.5 Hz, 1 H, Ar), 7.04 (d, J = 8.5 Hz, 1 H, Ar), 6.94 (d, J = 1.5 Hz, 1 H, Ar), 6.80 (d, J = 8.5 Hz, 2 H, Ar), 3.76 (s, 3 H, ArOCH_3), 3.55 (s, 2 H, ArCH_2), 3.52 (s, 2 H, ArCH_2) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 175.8 (C=O), 175.6 (C=O), 158.7 (Ar), 150.6 (Ar), 145.6 (Ar), 131.5 (Ar), 131.5 (Ar), 129.8 (Ar), 129.1 (Ar), 127.2 (Ar), 123.8 (Ar), 123.7 (Ar), 117.5 (Ar), 114.2 (Ar), 56.4 (ArO*C*H_3), 41.1 (Ar*C*H_2), 40.1 (Ar*C*H_2) ppm. HRMS (ESI): calcd. for $C_{17}H_{15}O_6$ $[M - H]^-$ 315.0869; found 3315.0878.

1-{4-[5-({6,7-Dimethoxy-2-[(*S*)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinolin-1-yl}methyl)-2-methoxyphenoxy]benzyl}-6,7-dimethoxy-2-[(*S*)-1-phenylethyl]-1,2,3,4-tetrahydroisoquinoline (10): A solution of **8** (48.6 mg, 0.154 mmol) and **9** (131.5 mg, 0.461 mmol) in MeCN (1.5 mL), which contained Et_3N (0.128 mL) and BOP reagent (169.9 mg, 0.384 mmol), was stirred at room temp. for 16 h. The mixture was diluted with aqueous HCl (2 M), and the resulting solution was extracted with $CHCl_3$ (3 ×). The combined organic layers were washed with brine, dried with Na_2SO_4, and concentrated in vacuo to give a residue that was subjected to silica gel column chromatography (hexane/EtOAc, 1:3) to afford the coupling product (105.8 mg, 81%) as a colorless oil. The NMR spectra showed a mixture of the corresponding rotamers. $[\alpha]_D^{23}$ = –57.3 (c = 1.00, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2934, 1635, 1515 cm^{-1}. HRMS (ESI): calcd. for $C_{53}H_{58}N_2O_8$ $[M + H]^+$ 851.4271; found 851.4235. To a solution of the coupling product (48.6 mg, 57.1 μmol) in PhMe (1.0 mL) was added $POCl_3$ (0.4 mL) at room temp. The mixture was stirred and heated at reflux for 16 h and then concentrated in vacuo. The residue was redissolved in anhydrous MeOH (1.0 mL). To the resulting solution at –78 °C was added $NaBH_4$ (38.9 mg, 1.03 mmol). After stirring for 6 h, the mixture was diluted with aqueous HCl (2 M) at 0 °C, and the resulting solution was extracted with $CHCl_3$. The organic layer was dried with Na_2SO_4 and concentrated in vacuo to give a residue, which was subjected to preparative TLC (hexane/EtOAc, 2:1) to afford **10** (43.0 mg, 92%) as a white solid. $[\alpha]_D^{23}$ = +59.2 (c = 1.00, $CHCl_3$). IR (film): $\tilde{\nu}$ = 3060, 3026, 2964, 2934, 2835, 1609, 1507 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.16 (m, 6 H, Ar), 7.05 (m, 4 H, Ar), 6.87 (d, J = 8.5 Hz, 2 H, Ar), 6.85 (d, J = 8.5 Hz, 1 H, Ar), 6.77 (d, J = 8.5 Hz, 2 H, Ar), 6.71 (dd, J = 8.5, 2 Hz, 1 H, Ar), 6.62 (d, J = 2 Hz, 1 H, Ar), 6.59 (s, 1 H, Ar), 6.56 (s, 1 H, Ar), 5.97 (s, 1 H, Ar), 5.95 (s, 1 H, Ar), 3.85 (s, 3 H, ArOCH_3), 3.848 (s, 3 H, ArOCH_3), 3.85 (s, 3 H, ArOCH_3), 3.82 (s, 3 H, ArOCH_3), 3.7 (m, 4 H), 3.58 (m, 3 H), 3.56 (m, 3 H), 3.38–3.12 (m, 4 H), 3.04 (dd, J = 7, 14 Hz, 1 H), 3.0–2.8 (m, 3 H), 2.71 (dd, J = 7, 14 Hz, 1 H), 2.66 (dd, J = 7, 14 Hz, 1 H), 2.43 (m, 2 H), 1.34 (m, 6 H, CCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.3 (Ar), 149.8 (Ar), 147.3 (Ar), 147.3 (Ar), 146.5 (Ar), 146.47 (Ar), 146.43 (Ar), 146.3 (Ar), 144.6 (Ar), 134.1 (Ar), 133.3 (Ar), 131.0 (Ar), 129.74 (Ar), 129.66 (Ar), 128.3 (Ar), 128.27 (Ar), 127.4 (Ar), 126.7 (Ar), 126.6 (Ar), 126.1 (Ar), 122.6 (Ar), 116.7 (Ar), 112.4 (Ar), 111.5 (Ar), 111.4 (Ar), 60.7 (CHN), 60.6 (CHN), 59.2 (ArO*C*H_3), 56.3 (ArO*C*H_3), 55.9 (ArO*C*H_3), 55.8 (ArO*C*H_3), 55.7 (ArO*C*H_3), 41.5 (CH_2N), 41.4 (CH_2N), 39.7 (Ar*C*H_2), 39.6 (Ar*C*H_2), 23.9 (Ar*C*H_2), 22.3 (C*C*H_3), 22.2 (C*C*H_3) ppm. HRMS (ESI): calcd. for $C_{53}H_{59}N_2O_6$ $[M + H]^+$ 819.4373; found 819.4401.

***O*-Methylthalibrine (1):** A solution of **10** (11.7 mg, 14.3 μmol) and 37% aqueous HCHO (0.10 mL, 1.42 mmol) in EtOAc (0.45 mL) and MeOH (0.75 mL), which contained catalytic $Pd(OH)_2$, was stirred under hydrogen for 23 h. Filtration followed by concentration of the filtrate in vacuo gave a residue that was subjected to preparative TLC ($CHCl_3$/MeOH, 12:1) to afford **1** (5.2 mg, 57%) as a colorless oil. $[\alpha]_D^{23}$ = +76.2 (c = 0.36, $CHCl_3$). IR (film): $\tilde{\nu}$ = 2996, 2935, 2837, 1610, 1508 cm^{-1}. ^1H NMR (400 MHz, $CDCl_3$): δ = 7.00 (d, J = 8.4 Hz, 2 H, Ar), 6.88 (d, J = 8.4 Hz, 1 H, Ar), 6.84 (dd, J = 8.4, 2 Hz, 1 H, Ar), 6.77 (d, J = 8.4 Hz, 2 H, Ar), 6.70 (d, J = 2 Hz, 1 H, Ar), 6.56 (s, 1 H, Ar), 6.52 (s, 1 H, Ar), 6.04 (s, 1 H, Ar), 5.97 (s, 1 H, Ar), 3.83 (s, 3 H, ArOCH_3), 3.81 (s, 3 H, ArOCH_3), 3.79 (s, 3 H, ArOCH_3), 3.77–3.64 (m, 2 H), 3.59 (s, 3 H, ArOCH_3), 3.56 (s, 3 H, ArOCH_3), 3.25–3.12 (m, 4 H), 2.89–2.73 (m, 7 H), 2.6 (m, 1 H), 2.57 (s, 3 H, NCH_3), 2.52 (s, 3 H, NCH_3) ppm. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 156.5 (Ar), 149.8 (Ar), 147.54 (Ar), 147.50 (Ar), 146.52 (Ar), 146.47 (Ar), 144.6 (Ar), 133.4 (Ar), 132.6 (Ar), 130.9 (Ar), 128.3 (Ar), 126.1 (Ar), 125.7 (Ar), 122.5 (Ar), 116.8 (Ar), 112.5 (Ar), 111.2 (Ar), 111.19 (Ar), 111.1 (Ar), 110.9 (Ar), 65.0 (CHN), 64.8 (CHN), 56.2 (ArO*C*H_3), 55.84 (ArO*C*H_3), 55.81 (ArO*C*H_3), 55.7 (ArO*C*H_3), 55.6 (ArO*C*H_3), 46.8 (CH_2N), 46.6 (CH_2N), 42.5 (NCH_3), 42.3 (NCH_3), 40.6 (Ar*C*H_2), 40.3 (Ar*C*H_2), 25.2 (Ar*C*H_2), 25.0 (Ar*C*H_2) ppm.

HRMS (ESI): calcd. for $C_{39}H_{47}N_2O_6$ $[M + H]^+$ 639.3434; found 639.3439.

Birch-Type Reduction: To a solution of liquid NH_3 (10 mL) that contained Na (60.5 mg) at –78 °C was added dropwise a solution of **1** (3.9 mg) in 1,4-dioxane (3 mL). After stirring for 2 h, the mixture was diluted with saturated aqueous NH_4Cl, and the resulting mixture was stirred at room temp. for an additional 2 h. The mixture was extracted with $CHCl_3$. The organic layer was concentrated in vacuo to give a residue that was subjected to preparative TLC ($CHCl_3$/MeOH/$HNEt_2$, 10:1:0.1) to afford **11** (0.5 mg, 26%) as a colorless oil $\{[\alpha]_D^{20} = +117$ ($c = 1.0$, $CHCl_3$)$\}$ and **12** (2.0 mg, quantitative) as a colorless oil $\{[\alpha]_D^{20} = +83.7$ ($c = 0.35$ $CHCl_3$)$\}$.

Supporting Information (see footnote on the first page of this article): Experiments of synthetic approach to **1** by reduction of chlorine substituents at the final stage, copies of the ^1H and ^{13}C NMR spectra, and HPLC data.

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