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Electrochemical construction of the diaryl ethers: a synthetic approach to *o*-methylthalibrine

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ABSTRACT

Electrochemical dimerization of halogenated *p*-hydroxyphenylacetic acid derivatives followed by Zn reduction provided the corresponding diaryl ethers. Manipulation of the reduction step using several procedures increased its efficiency, which enabled the construction of *o*-methylthalibrine, an isoquinoline-class alkaloid.

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1. Introduction

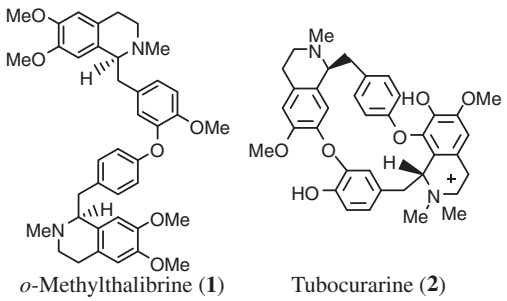
o-Methylthalibrine (**1**) is a bisbenzylisoquinoline alkaloid, isolated from the plant *Thalictrum revolutum* DC,[1] which is used as a folk medicine in central Asia. In addition to antimalarial and cytotoxic activities, its structural similarity to tubocurarine alkaloid (**2**) prompted us to initiate a synthetic study as part of our ongoing phenolic oxidation approach to both natural and unnatural bioactive substances (Fig. 1).[2] In the key step of this approach, anodic or thallium(III) salt oxidation of the appropriately dihalogenated phenol derivatives (**A**) will effect one-electron oxidation to provide the corresponding dimers (**B**), providing the expected diaryl ethers[3] (**C**) on treatment with Zn powder in the presence of AcOH (Scheme 1). Two halogen atoms located at *ortho* positions play an important role in controlling the oxidation potential of the phenol functions and regioselectivity of the coupling reactions. The tandem protocol developed in our laboratory enabled the total synthesis of isodityrosine and the related natural products. However, improvement of Zn reduction was required to circumvent undesirable adsorption of substrates to the metal powder, and to avoid problematic activation of Zn powder by washing in aqueous acidic solution. Herein, we report the synthesis of **1** along with a new manipulation of Zn reduction.[4]

In the retrosynthetic analysis of the target alkaloid **1**, oxidative dimerization of the phenol derivatives carrying (1) a dihydroisoquinoline residue (**3**), (2) an isoquinoline precursor (**4**), along with (3) a simple dihalogenated *p*-hydroxyphenylacetate (**5**) would provide the corresponding coupling product **1′**. Although use of the former two substrates seemed to be shorter synthetic processes to the target **1**, the attached additional aromatic moieties were anticipated to impede clear phenolic oxidation.[5] Indeed, a previous study using **3** (X = Br, P = Ac) and **4** (X = Br) synthesized by the standard procedure from *p*-hydroxyphenylacetic acid (**6**) indicated that their anodic oxidation reactions provided complex mixtures.[6]

Accordingly, the halogenated derivative **5** was examined under anodic oxidation conditions (Table 1). Using bromine substituents (**5-Br**), anodic oxidation under acidic conditions provided the desired diaryl ether (**7-Br**)[11] in yields of 17–35%, along with the corresponding two-electron oxidation product **8-Br**, whereas the pyridine condition (entry 1) gave the products in very low yields. Undesirable oxidative polymerization caused low material balances. However, the reactions at 0 °C (entries 6 and 8) provided the products in relatively good yields, as well as recovery of the starting materials. In the following entries (9–14) using chlorine substituents (**5-Cl**), the reaction temperature was fixed at 0 °C, and the optimized yield of **7-Cl**[11] was obtained in entry 14.[7]

2. Reductive procedure in the preparation of the diaryl ethers

In our previous investigation, we employed the Zn powder with AcOH conditions, which enabled the synthesis of natural products carrying the diaryl ether moiety (Scheme 2). However, the reduction requires an excess amount of Zn powder, which often causes marked adsorption of substrates and lowers the isolated yield. In



o-Methylthalibrine (**1**) Tubocurarine (**2**)

Figure 1. *o*-Methylthalibrine (**1**) and tubocurarine (**2**).

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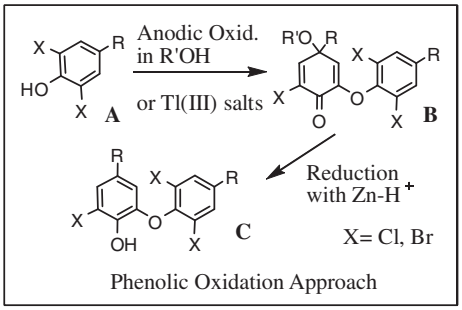
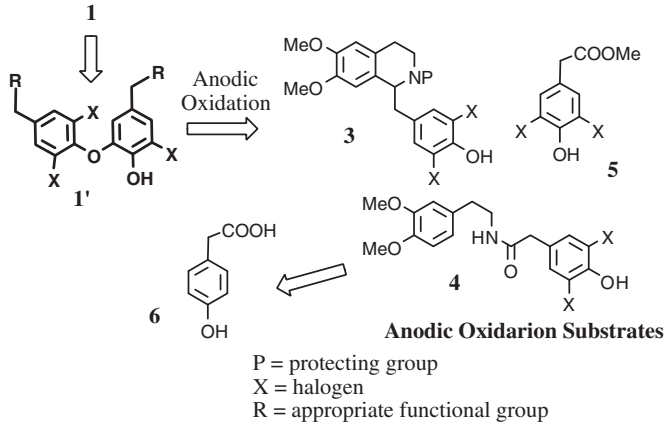
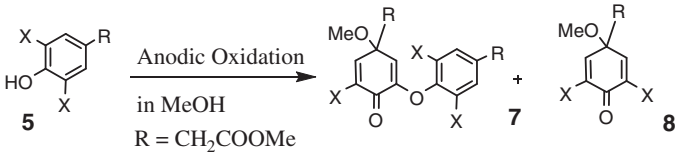




Scheme 1. Phenolic oxidation approach and retrosynthetic analysis of **1**.

Table 1
Anodic oxidation[a] of the dihalogenated phenols **5**



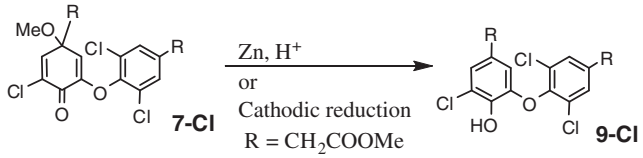
Entries[b]	X	Anode	Additive	*F* (mol)	Yields (%)		
					7	**8**	**5**
1	Br	Pt	L, pyr.	3	3	3	—
2		Pt	L, H	3	33	18	—
3		Pt	H	3	17	16	—
4		C	L, H	2	35	12	—
5		C	L, H	3.5	31	3	—
6		C	L, H	3	27	26	35
7		Pt	L, H	2.5	24	44	7
8		Pt	L, H	2.5	23	34	17
9	Cl	C	H	2.5	52	17	—
10		Pt	L, H	1.5	47	20	—
11		Pt	L, H	3.5	43	2	—
12		Pt	H	2	53	8	—
13[c]		Pt	H	3	51	Trace	—
14		Pt	H	3	60	—	—

[a] General procedure: compound **5** (30–50 mg scale, 10 mmol concentration) in MeOH in the presence of additives [$LiClO_4$ (L) 0.1 M concentration, $HClO_4$ (H) 0.1 M concentration, or pyridine 3 equiv mol vs **5**] was oxidized under constant current electrolysis conditions (CCE, 10 mA/cm^2, anode = glassy carbon beaker: 25 mL (C), Pt net $3\phi \times 2.5$ cm (Pt); cathode = Pt wire 0.1×1 cm). The reaction mixture was partitioned between EtOAc and H_2O. The organic layer was dried and purified by preparative TLC to give the products.

[b] The reactions were performed at room temperature in entries 1–5 and 7, and at 0 °C in entries 6 and 8–15.

[c] This entry used 2 mmol concentration.

a related reduction during the synthesis of isodityrosine,[8] it was observed that a Zn electrode dipped in acidic solution showed the same effect as Zn powder, and the following simple rinsing



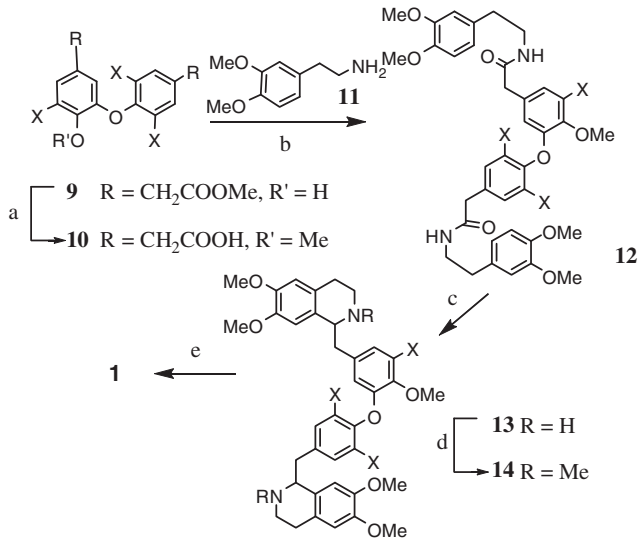
Scheme 2. Reduction of **7**.

of the electrode gave the desired diaryl ether in high yield. Using the Zn-plate procedure for **7-Cl**, the desired diaryl ether **9-Cl**[11] was obtained in 61% yield.[10a] To acquire better yields of the reduction, the dichlorodienone **7-Cl** was subjected to electrolysis using Zn plate to give the diaryl ether in 99% yield.[10b] Under the same reaction conditions, **7-Br** was converted into the corresponding **9-Br**[11] in 60% yield. This result indicated that electrochemically accumulated Zn at the cathode surface contributed to the reaction efficiency. Indeed, when electrolysis was performed using a Pt-electrode in the presence of a zinc ion, the diaryl ether was produced in 85% yield.

As mentioned above, the anodic oxidation and the following reduction including new Zn-plate and electrochemical methods enabled adequate supply of the diaryl ether derivative **9**. We then applied our method to the production of *o*-methylthalibrine (**1**).

3. Synthetic approach to *o*-methylthalibrine (1) from the diaryl ethers (9)

The free phenol group of **9**[9] was protected as a methyl ether under standard conditions, followed by alkaline hydrolysis to give the dicarboxylic acid **10** in high yield, which on condensation with dimethoxytyramine (**11**) using the BOP reagent [(benzotriazol-1-yloxy)-tris(dimetylamino)phosphonium hexafluorophosphate], and Et_3N provided **12**. Spontaneous construction of both the isoquinoline moieties was performed by the Bischler–Napieralski protocol using $POCl_3$, followed by $NaBH_4$ reduction of the newly produced iminium salts, leading to **13**. After introduction of *N*-methyl functions, the halogens in **14** were removed by hydrogenolysis. In contrast to unsuccessful results in the case of the chlorines, the bromine derivative was smoothly transformed into the desired plane structure of **1** (Scheme 3).



Scheme 3. Reagents and conditions: (a) (i) MeI, K_2CO_3, DMF (X = Br 100%, X = Cl 70%); (ii) NaOH (X = Br 100%, X = Cl 100%); (b) BOP reagent, Et_3N, **11** (X = Br 100%, X = Cl 69%); (c) $POCl_3$, PhMe, then $NaBH_4$ (X = Br 100%, X = Cl 34% in two steps); (d) $(CH_2O)_n$, AcOH, $NaBH_3CN$ (X = Br 100%, X = Cl 100%); (e) H_2, 5% Pd/C (X = Br 48%).

In conclusion, the zinc-mediated reduction of the oxidized derivative was improved by an electrochemical procedure for efficient conversion to the expected diaryl ether derivative using the environmentally benign newly manipulated zinc reduction protocol. The dimeric products were successfully converted into the target framework of **1**. Further investigation to obtain the target molecule in optically active form is in progress.

Acknowledgments

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4. Part of this work was presented in ECS Meeting, Vienna, 2009.
5. In the case of verbenachalcone (Ref. 2e), the oxidation of phenolic function attached with another aryl group gave a complex mixture.
6. Upon using **4** (X = Cl), the desired product was obtained up to 37% yield, however, this process was not adopted for the following conversion in low yields.
   Preparation of **5** *from* **6**: **5**-**Br**, Br_2, MeOH (100%); **5**-**Cl**, (i) cat. H_2SO_4, MeOH; (ii) SO_2Cl_2, AcOH, then Zn (62% in two steps). Compounds **3** and **4** were synthesised by essentially the same procedure as depicted in Scheme 3.
7. When **5**-**Br** was subjected to the same conditions as entry 14, **7**-**Br** was produced in 28% yield. In the anodic oxidation of **5**, the chloro derivative provided better result than that of the bromo derivative, however, the latter exhibited effective conversion to the target molecule.
8. Uno, K.; Tanabe, T.; Nishiyama, S. *ECS Trans.* **2009**, *25*, 91–95.
9. For the preparative procedure, **9** was synthesized by the successive two-step manipulation of **5**: **9**-**Br**, 36%, **9**-**Cl**, 66% yields, respectively.
10. (a) A solution of **7**-**Cl** (30.0 mg, 0.065 mmol) in MeOH (12.5 mL) and AcOH (0.4 mL) was kept in the presence of a couple of Zn plates (15 × 20 × 0.5 mm). The reaction was gradually warmed from 0 °C to ambient temperature. After being reacted overnight, the mixture was partitioned between $CHCl_3$ and H_2O. The organic layer was washed with brine, dried, then purified by preparative TLC (hexane/EtOAc = 3:1) to give **9**-**Cl** (17.1 mg, 61%).; (b) A solution of **7**-**Cl** (24.5 mg, 0.053 mmol) in MeOH (21 mL), AcOH (0.4 mL) and 60% aq $HClO_4$ (0.2 mL) was electrolyzed under the CCE conditions (anode, cathode = Zn plate 15 × 20 × 0.5 mm, −10 mA, undivided cell). The reaction was gradually warmed from 0 °C to ambient temperature. After being reacted overnight, work-up provided **9**-**Cl** (22.7 mg, 99%).; (c) A solution of **7**-**Cl** (31.2 mg, 0.067 mmol) and $Zn(OAc)_2{\cdot}H_2O$ (210 mg, 0.96 mmol) in MeOH (10 mL) and 60% aq $HClO_4$ (0.2 mL) was setted to a cathode chamber (Pt plate electrode of the H-type divided cell, EOS-30, Technosigma) with anion exchange membrane (Neosepta AHA), and Na_2SO_4 (284 mg) in H_2O (10 mL) in an anode chamber (Pt wire electrode). After being reacted overnight, the mixture was worked up to give **9**-**Cl** (24.8 mg, 85%).
11. *Selected data:* Compound **7**-**Cl**: IR (film) 1736, 1692 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 2.68 (1H, d, *J* = 14 Hz), 2.73 (1H, d, *J* = 14 Hz), 3.18 (3H, s), 3.61 (2H, s), 3.64 (3H, s), 3.75 (3H, s), 5.51 (1H, d, *J* = 2.4 Hz), 7.17 (1H, d, *J* = 2.4 Hz), 7.34 (2H, s); HRFABMS Calcd for $C_{19}H_{17}O_7{}^{35}Cl_3$: 462.0062 (M), found *m*/*z* 462.0040. Compound **7**-**Br**: IR (film) 1734 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 2.67 (1H, d, *J* = 15 Hz), 2.72 (1H, d, *J* = 15 Hz), 3.22 (3H, s), 3.61 (2H, s), 3.65 (3H, s), 3.75 (3H, s), 5.49 (1H, d, *J* = 2.4 Hz), 7.45 (1H, d, *J* = 2.4 Hz), 7.54 (2H, s); HRFABMS Calcd for $C_{19}H_{18}O_7{}^{79}Br_3$ (M+1): 593.8564, found *m*/*z* 593.8524. Compound **9**-**Cl**: IR (film) 1735 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 3.41 (2H, s), 3.63 (2H, s), 3.65 (3H, s), 3.76 (2H, s), 6.06 (1H, s), 6.29 (1H, d, *J* = 2 Hz), 7.15 (1H, d, *J* = 2 Hz), 7.56 (2H, s); HRFABMS Calcd for $C_{18}H_{16}O_6{}^{35}Cl_2{}^{37}Cl$: 569.8373 (M+1), found *m*/*z* 569.8357. Compound **9**-**Br**: IR (film) 1734 cm^{-1}; δ_H ($CDCl_3$, 400 MHz) 3.41 (2H, s), 3.63 (2H, s), 3.65 (3H, s), 3.76 (2H, s), 6.06 (1H, s), 6.29 (1H, d, *J* = 2 Hz), 7.15 (1H, d, *J* = 2 Hz), 7.56 (2H, s); HRFABMS Calcd for $C_{18}H_{15}O_6{}^{81}Br_3$: 569.8373 (M), found *m*/*z* 569.8357.