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Tetrahedron Letters 45 (2004) 3477–3480

Tetrahedron Letters

A total synthesis of verbenachalcone, a bioactive diaryl ether from *Verbena littoralis*

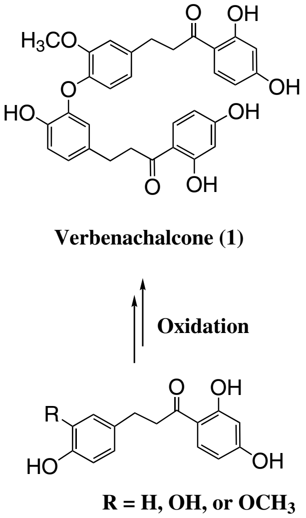
Takamasa Tanabe, Fuminao Doi, Takahisa Ogamino and Shigeru Nishiyama*

Department of Chemistry, Faculty of Science and Technology, Keio University, Hiyoshi 3-14-1, Kohoku-ku, Yokohama 223-8522, Japan

Received 4 February 2004; revised 23 February 2004; accepted 27 February 2004

Abstract—Verbenachalcone **1**, isolated from the aerial part of *Verbena littoralis* H. B. K. (Verbenaceae), has successfully been synthesized by employing anodic oxidation of the phenol derivative **3**, as the key step. The bromine and chlorine substituents of **3** effected regioselective introduction of a methoxy group, as well as modulating the oxidation reaction. A flow-cell type apparatus of anodic oxidation provided the desired diaryl ether **4** in good yield.

Verbenachalcone **1**, an activator of nerve growth factor (NGF)-mediated neurite outgrowth of PC12D cells, possesses a dimeric structure linked through the diaryl ether linkage.[1] From the viewpoint of phenolic oxidation, a biosynthesis of this molecule might involve a one-electron oxidation process, as depicted in Scheme 1.



Scheme 1.

In this context, we have extensively investigated biomimetic oxidation by employing electrochemical or thallium(III) oxidation of halogenated phenols, leading to the corresponding diaryl ethers or spiro-type products.[2] However, construction of the diaryl ether attached with an alkoxyl group at the *ortho*-position of the phenol group, would be accompanied with difficulties, not to provide the desired diaryl ether but to produce dienone-type products, owing to high-oxidation potential, which preferred the two-electron oxidation process. For instance, anodic oxidation of eugenol was reported to give the acetal **A** as a major product, which underwent Diels–Alder reaction to yield asatone-type products (Scheme 2).[3] On the other hand, upon using basic conditions, the diaryl derivative **B** was obtained through the one-electron oxidation, instead of the diaryl ether **C**. The anodic oxidation seemed to require an additional factor, although regioselective coupling of aryl halides and phenols under the Ullmann-type conditions might assemble the desired diaryl ether.[4] In contrast to such problems in our anodic oxidation chemistry, the methoxy-diaryl ether functions have been found in natural products, such as diarylheptanolides from *Juglans mandshurica*.[5] As a new electrochemical access to construct these functions, we utilized a mixed-halogenated phenol (type-**D**), which provided the dimer (type-**E**) by oxidative coupling exclusively at the Br position, followed by Zn reduction, as depicted in Scheme 2.[6] Although synthesis of verbenachalcone **1** by a conventional method was recently reported,[7] we describe

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Keywords: Verbenachalcone; Anodic oxidation; *Verbena littoralis* H. B. K.; PC12D cells; Diaryl ether.

* Corresponding author. Tel./fax: +81-45-566-1717; e-mail: nisiyama@chem.keio.ac.jp

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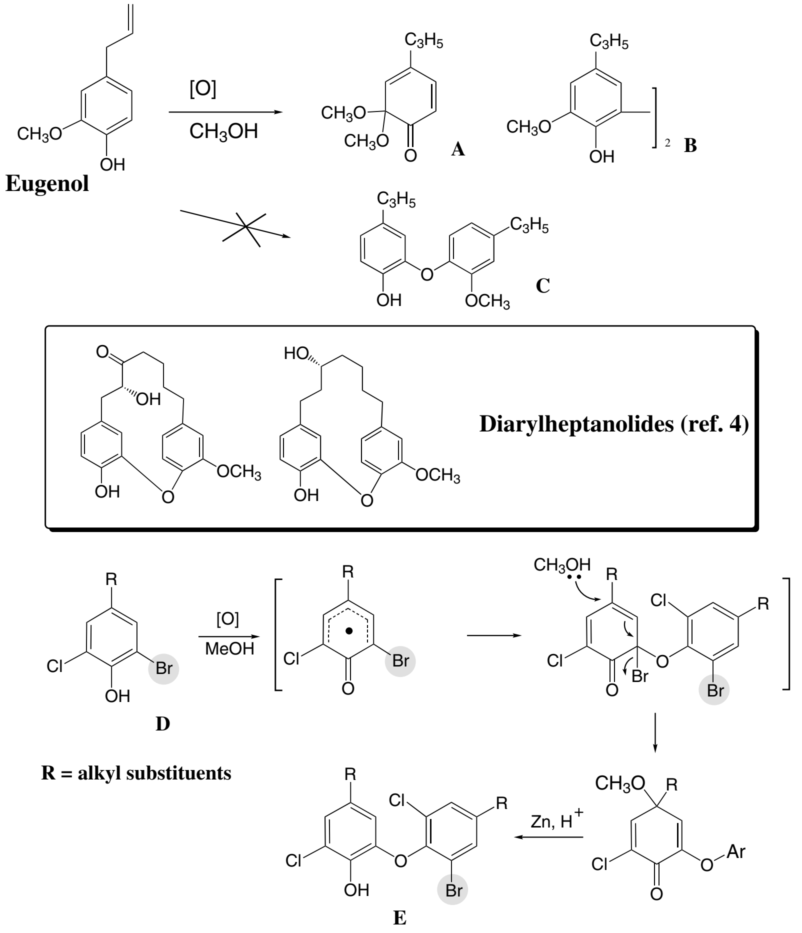
doi:10.1016/j.tetlet.2004.02.154

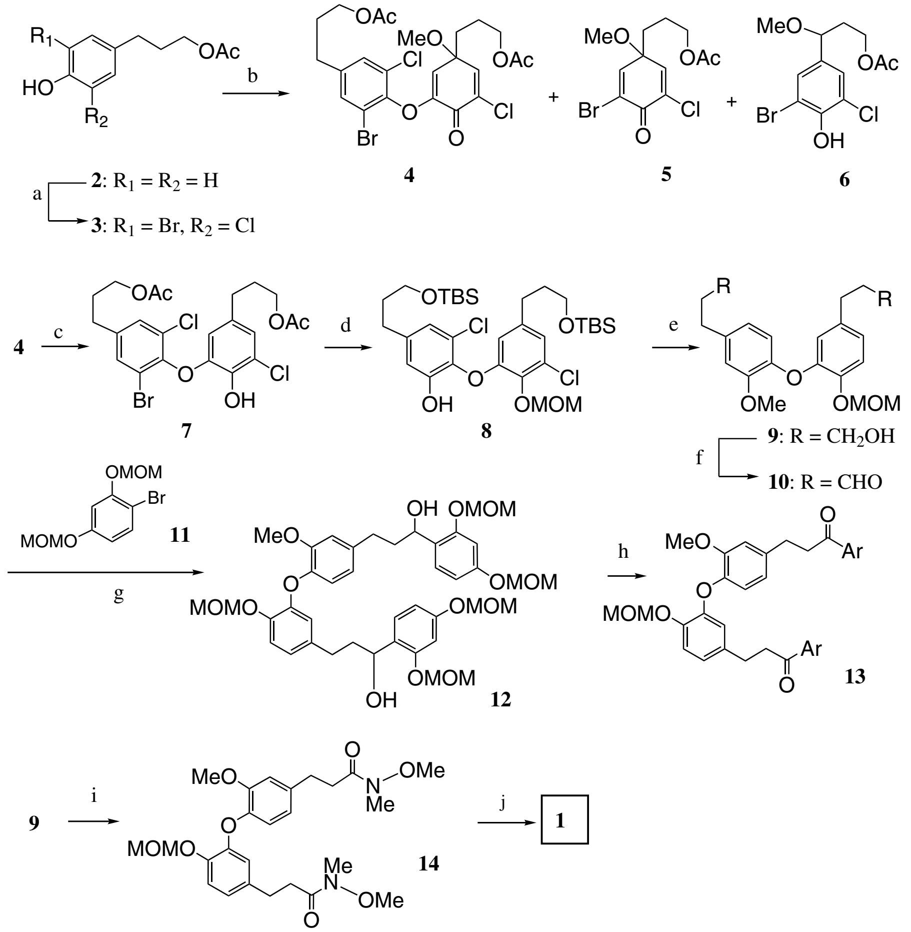


Scheme 2.

herein its synthesis by our own phenolic oxidation protocol.

Compound **3** without the terminal tri-substituted phenyl ring, was employed as a substrate of anodic oxidation to prevent undesired side-reactions (Scheme 3). This compound was produced by the two-step halogenation reaction of **2**[8] in 64% yield. Among anodic oxidation of **3** under the conditions depicted in Table 1, the expected **4**[9] was obtained in all entries, although undesired **5** and **6**[10] were co-produced. Addition of pyridine neutralized the acidity of the reaction solution. The lowered oxidation potential under the basic conditions, preferentially produced the radical species, which underwent dimerization to give the diaryl ether **4** (upon comparison of entry 3 with entry 2, pyridine effected production of **4** in better yield). Although **4** was produced in ca. 50% yield, the low substrate concentrations (entries 4 and 5) would not be suitable to large scale experiments. When using a diamond electrode as an anode, **5** and **6**, which were produced through cationic intermediates, were preferentially obtained even in the presence of pyridine (entry 6). The optimized yield was attained, when using a flow-cell apparatus, which suppressed the undesired two-electron oxidation leading to **5** and **6**, as well as other side reactions (entry 7). In particular, the 62% yield in this entry was obtained, upon using a 3g portion of **3**. Compound **4** in hand was submitted to Zn reduction to give the diaryl ether **7**. After manipulation in three steps to exchange the protecting groups (quant), followed by introduction of a borate group, treatment with alkaline H_2O_2, gave phenol **8** in 82% yield. Successive methylation of the phenol group (quant), removal of the chlorine atoms under hydrogen transfer conditions (84%), and TBAF-treatment (quant), provided the corresponding alcohol **9**, which on oxidation produced dialdehyde **10** in 81% yield. Upon treatment with a lithio derivative of **11**, **10** underwent the expected coupling to give the benzyl alcohol **12** in 27% yield, which on oxidation gave quantitatively the protected varbenachalcone **13**. To overcome the low yield of **12**, alcohol **9** was submitted to PDC oxidation, followed by conversion into the corresponding Weinreb amide **14**. Successful coupling with a lithio derivative of **11**, produced **13** in 64% yield, which on acidic hydrolysis provided **1** in quantitative yield. Under the full range of spectroscopic data, the synthetic sample was superimposable to the natural **1**.

In conclusion, anodic oxidation of the mixed-halogenated phenol **3** in a gram scale using a flow-cell apparatus, provided the corresponding diaryl ether **4** in 62% yield. The Br substituent was selectively converted into a methoxy group, and further synthetic manipulation



Scheme 3. Reagents and conditions: (a) (i) SO_2Cl_2, $CHCl_3$, 64%; (ii) HBr_3-pyr., quant. (b) See Table 1. (c) Zn–AcOH, THF, 79%. (d) (i) MOMCl, Hünig base, CH_2Cl_2, quant; (ii) K_2CO_3, MeOH, quant; (iii) TBSCl, Imd, quant; (iv) $B(OMe)_3$, *n*-BuLi; (v) 3M NaOH, H_2O_2, 82% in two steps. (e) (i) MeI, K_2CO_3, DMF, quant; (ii) Pd–C, HCO_2NH_4, 60 °C, EtOH, 84%; (iii) TBAF, THF, quant. (f) Dess-Martin oxid., CH_2Cl_2, 81%. (g) **10**, *n*-BuLi, THF, 27%. (h) TPAP, NMO, MS4A, CH_2Cl_2, quant. (i) (i) PDC, DMF, 52%; (ii) Me(MeO)NH, WSCl, HOBt, Et_3N, CH_2Cl_2, 95%. (j) (i) **10**, *n*-BuLi, THF (64%); (ii) TsOH, MeOH, quant.

Table 1. Anodic oxidation (CCE at 20 mA) of the phenol **3**

Entries	Conditions[e]			Products (%)	
	Potential (V vs SCE)	Substrate conc. (mM)	Solvents	**4**	**5** + **6**
1[a]	1.0–1.5	10	MeOH	16	23
2[b]	1.0–1.2	10	MeOH	26	4
3[b]	0.8–0.9	10	MeOH, pyridine	37	7
4[b]	1.1–1.3	2	MeOH, pyridine	51	8
5[b]	1.1–1.4	0.5	MeOH, pyridine	50	12
6[c]	2.0–2.5[f]	10	MeOH, pyridine	3	30
7[d]	2.95–3.0	10	MeOH, pyridine	62	—

[a] Glassy carbon beaker (anode)–Pt wire (cathode).

[b] Pt net (anode)–Pt wire (cathode).

[c] Diamond electrode (anode)–Pt wire (cathode).

[d] Flow-cell carbon sheet (anode)–Pt wire (cathode); flow rate, 0.4 mL/min.

[e] Supporting salt $LiClO_4$. Constant current electrolysis (CCE) at 20 mA, 3 F/mol.

[f] Constant current at 10 mA.

provided verbenachalcone **1**. This methodology would open up a new access to synthesis of bioactive substances carrying diaryl ether moieties with adjacent methoxy or other functional groups.

Acknowledgements

This work was supported by Grant-in-Aid for the 21st Century COE program ‘KEIO Life Conjugate

Chemistry', as well as Scientific Research C from the Ministry of Education, Culture, Sports, Science, and Technology, Japan. The authors are indebted to Professor Y. Einaga and Mr. M. Chiku of the same Department for the preparation of a diamond electrode.

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9. **4**: IR (film) 2939, 1737, and 1693 cm^{-1}; ^{1}H NMR (400 MHz, CDCl$_3$) δ 1.60 (2H, complex), 1.78 (2H, complex), 2.00, (2H, complex), 2.03 (3H, s), 2.07 (3H, s), 2.70 (2H, t, $J = 7.8$ Hz), 3.21 (3H, s), 4.00 (2H, t, $J = 6.4$ Hz), 4.12 (2H, t, $J = 6.4$ Hz), 5.31 (1H, d, $J = 2.9$ Hz), 6.95 (1H, d, $J = 2.9$ Hz), 7.28 (1H, d, $J = 2.0$ Hz), and 7.40 (1H, d, $J = 2.0$ Hz); ^{13}C NMR (100 MHz, CDCl$_3$) δ 20.9, 20.9, 23.0, 29.6, 31.3, 36.7, 53.1, 63.3, 63.7, 117.3, 121.0, 128.1, 129.8, 130.1, 132.0, 133.4, 141.7, 144.5, 147.0, 148.4, 170.7, 170.8, and 182.7. Calcd for $C_{23}H_{25}$ $^{79}Br^{35}Cl_2O_7$ (M$^+$) 562.0158, found: m/z 562.0156.
10. Compounds **5** and **6** were obtained as an inseparable mixture (ca. 5 ∼ 3:1=**5/6**). Their structures and ratio were determined by ^{1}H NMR spectrum of the mixture.