Synthesis of Bioactive Sesquiterpene Heliannuol E Involving a Ring-Expansion Reaction of Spirodienones

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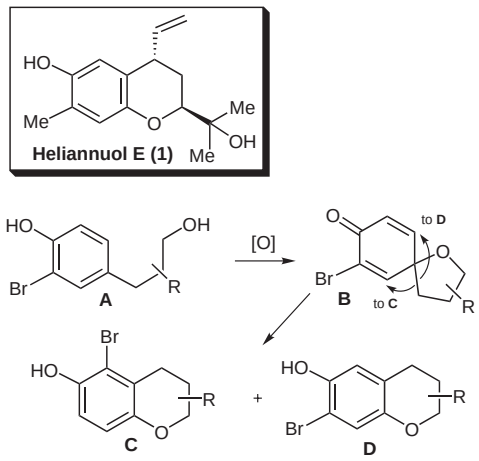
Abstract: A heliannane-type sesquiterpene, heliannuol E (**1**), has been successfully synthesized. The key step was conversion of the electrochemically produced spiro compounds (**8**, and **18**) into the corresponding dihydrobenzopyrans (**11**, **12**, **19**, and **20**) by a selective ring expansion process.

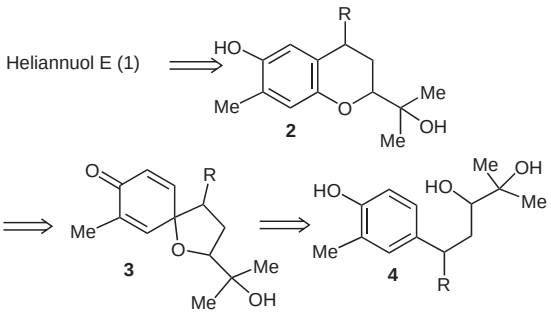
Key words: heliannuol E, anodic oxidation, sesquiterpene, dihydrobenzopyran, two-electron oxidation

Heliannuol E **1**, isolated from the aqueous extracts of *Helianthus annuus* L. cv. SH-222, might contribute to the allelopathogenic action of cultivar sunflowers,[1] which would open up the possibility of new-type agricultural chemicals. This sesquiterpene in an optically active form, was ingeniously synthesized by Shishido et al.,[2] employing a similar route to its proposed biogenesis.[3]



Scheme 1

From our extensive electrochemical investigation towards the total synthesis of natural products,[4–6] it was observed that the spiro derivative **B** generated by anodic oxidation of the corresponding monobromophenol **A**,[7] was converted under Lewis acid conditions into dihydrobenzopyrans **C** and **D** (Scheme 1). The regioselectivity in the ring expansion reaction (**B** to **C** and/or **D**) was controlled by steric hindrance between a bromine and substituents R of the 3-hydroxypropyl side-chain.[8] While the ratio of **C** and **D** was 2:3 at the most in the case of R = H, such bulky substituents as Fmoc-amino, *i*-Pr, *i*-Bu, *gem*-dimethyl groups, provided the type-**D** products in 70–77% yields. To expand the utility of this rearrangement into natural products synthesis, we demonstrate herein the synthesis of **1**. According to a fundamental retrosynthetic analysis (Scheme 2), the target molecule would be produced by the regioselective conversion of **3** into **2**, which might be obtained by the two-electron oxidation of **4**. To accomplish this purpose, the effect of a methyl group in the aromatic ring, should be confirmed in the anodic oxidation leading to the spiro compound **3**, as well as in the ring expansion reaction to **2**.



Scheme 2

At the outset, anodic oxidation of **5**, synthesized in the usual way from *ortho*-cresol in 7 steps, was carried out as a model study to understand the chemical profile of the phenol derivatives carrying methyl groups in the oxidation. When **5** was oxidized under CCE conditions (anode: glassy carbon beaker, cathode: platinum wire, $LiClO_4$ as a supporting salt, MeOH or dioxane with/without 60% aq $HClO_4$ as a solvent), the spiro compound **6** was produced in very low yield under a wide range of reaction conditions attempted. After synthetic elaboration of the spiro-structure, we noticed an introduction of a halogen atom to the *ortho*-moiety of the phenol group to control the oxidation potential and the reaction mode.[4–6,9] Thus, compound **5** was treated with bromine to give **7** in 90% yield, which was submitted to the anodic oxidation by employing essentially the same procedure as described above (Table 1, Figure 1).

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Table 1 Anodic Oxidation of Bromophenol **7** under CCE Conditions[a]

Entry	Condition V vs SCE(Fmol^{-1})	Solvent	Products, yield (%)		
			8	**9**	**10**
1	0.85–1.30 (1.7)	MeOH	21	32	5
2	1.20–1.30 (2.0)	MeOH	43	29	13
3	1.20–1.30 (2.0)	MeOH–60% aq $HClO_4$ (5:1)	24	–	30
4	1.60–1.80 (8.2)	Dioxane–60% aq $HClO_4$ (5:1)	50	–	–

[a] Concentration of the substrate **7**: 1.2 mM. Supporting salt: 0.1 M concentration $LiClO_4$.

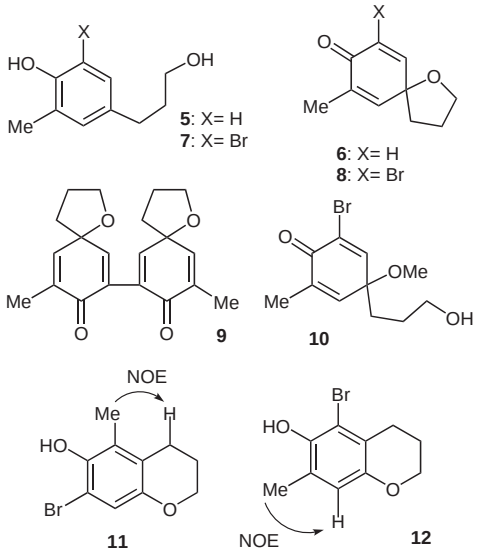
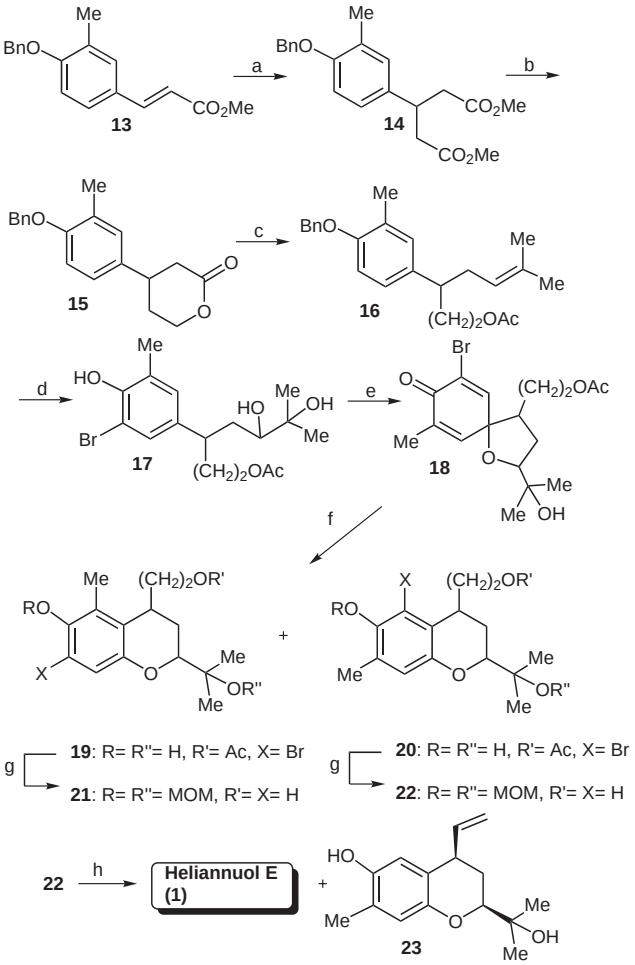


Figure 1

While the expected spirodienone **8**[13] was obtained in all of the entries,[10] entries 1–3 involved the undesired radical coupling product **9** and the dienone **10** involving a MeO group derived from the solvent. Ultimately, despite the low current efficiency, acidic conditions in dioxane–60% aq $HClO_4$ (entry 4) effectively induced the two-electron oxidation to generate a cation, which was captured by the terminal hydroxyl group to give **8** as the sole product. In the next stage, the spiro derivative **8** was submitted to the Lewis acid-promoted rearrangement ($BF_3{\cdot}OEt_2/CH_2Cl_2$, r.t.). Although the reaction conditions were not optimized, two rearranged products **11**[13] and **12**[13] were obtained in 6 and 33% yields, respectively. The NOE experiments indicated that the expected **12** was preferentially produced. In the preceding paper using *ortho*-bromo phenol derivatives, steric repulsion of substituents controlled the direction of the rearrangement: the benzylic carbon was shifted to the opposite side of the Br group. In contrast, the rearrangement of *ortho*,*ortho*-bromomethyl derivatives (ex. **8**) proceeded to the Br side. One reason for this selectivity might be directed by the electron-withdrawing property of the bromine atom, along with the donating property of a methyl group.



Scheme 3 *Reagents*: a. i) Dimethyl malonate, DBU/MeOH, reflux; ii) DMSO, NaCl/reflux, 84% in two steps; b. i) KOH (98%); ii) $(PhO)_2P(O)Cl$, Et_3N, then MeOH, pyridine; iii) $BH_3{\cdot}THF$; CSA/PhH (87% in four steps); c. i) DIBALH; ii) *i*-$PrPh_3PI$, *n*-BuLi; iii) Ac_2O, pyridine (74% in three steps); d. i) OsO_4; ii) H_2, Pd-C; iii) pyridine·HBr_3 (90% in three steps); e. Table 2; f. $BF_3{\cdot}OEt_2$ 75% as a mixture of **19** and **20**); g. i) H_2, Pd-C (quant.); ii) MOMCl, *i*-Pr_2NEt (67%); iii) K_2CO_3/MeOH (95%); h. i) MsCl, pyridine (quant.); ii) $O_2NC_6H_4SeCN$, $NaBH_4$, then 35% H_2O_2 (45%); iii) 6 M HCl (**1**: 56%, **23**: 36%).

Based on the observation mentioned above, a synthetic approach towards (+/–)-**1** was commenced with the Michael addition of dimethyl malonate to the cinnamic acid derivative **13**, followed by decarboxylation to give diester **14** (Scheme 3). After hydrolysis, compound **14** was converted in three steps into δ-lactone **15** in good yield. Compound **15** was treated with DIBALH, followed by Wittig reaction with isopropylidenetriphenylphosphorane and acylation to yield **16**. Successive three-step procedure produced the phenol **17**, which was submitted to the anodic oxidation (Table 2).

Table 2 Anodic Oxidation of **17** under CCE Conditions[a]

Entry	Condition V vs SCE (F mol^{-1})	Solvent	Yield of **18** (%)
1	1.10–1.20 (4.0)	MeOH	39
2	1.20–1.30 (2.0)	MeOH/60% aq $HClO_4$ (5/1)	6
3	1.55–1.75 (12.0)	Dioxane/60% aq $HClO_4$ (5/1)	35
4	1.50–1.60 (2.0)	MeCN	32
5	1.30–1.50 (2.0)	Acetone	61

[a] Substrate concentration: 1.5–2.0 mM. Supporting salt: entries 1–4 $LiClO_4$ (0.1 M), entry 5 Bu_4NClO_4 (0.1 M).

A crucial factor in the anodic oxidation was the selection of the reaction solvents: acetone effected oxidation leading to the spiro compound **18** (61% yield, entry 5),[11] rather than dioxane–$HClO_4$ conditions which provided good results in the case of **8**. The relatively low yields under the acidic conditions, might be owing to the acid-labile character of the tertiary hydroxyl group in the side-chain moiety. The Lewis acid treatment of the spirodienone **18** in hand, effected the desired rearrangement to give a mixture of the branched dihydrobenzopyrans **19** and **20** in 75% total yield. Unfortunately, diastereomers of both compounds could not be separated, and they were submitted to the following reactions without further separation. The mixture was hydrogenolized, followed by protection with MOM groups and solvolysis provided a chromatographically separable mixture of **21** and **22** (1:5). In spite of the diastereomeric mixtures of the aliphatic parts, their structures were spectroscopically confirmed by the *ortho*-coupling of the aryl protons (**21**), as well as the NOE effects of the benzylic protons with the aryl-methyl group (**21**) and the aryl protons (**22**). Finally, according to the reported procedure involving the selenium-supported dehydration by the Grieco protocol,[2,12] the major isomer **22** was successfully converted into the target molecule **1**,[13] along with the *cis*-isomer **23**[13] (**1**/**23** = 1.6:1).

In conclusion, the synthesis of the bioactive sesquiterpene (+/–)-heliannuol E **1** was accomplished by using conversion of spirodienone **18** electrochemically obtained into the dihydrobenzopyran **19**, **20** as the key step. The direction of the rearrangement was controlled by the bromine substituent at the *ortho*-position of a phenol group. Further synthesis of optically active **1** is under way.

Acknowledgment

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(8) Mori, K.; Yamamura, S.; Nishiyama, S. Tetrahedron **2001**, *57*, 5533. After this article was published, Plourde reported a similar oxidation of ortho-methoxyphenol **5** using such oxidants as $Pb(OAc)_4$, PIDA, or PIFA:Plourde, G. L. Tetrahedron Lett. **2002**, 43, 3597.
(9) The *ortho*-bromophenol derivative without methyl groups, might be available: the bromo substituent would be converted into the appropriate alkyl group. Although this method would require a rather longer synthetic process, the feasibility of the method is under consideration.
(10) Despite similar CV curves (first peak: ca. 1.05 V vs SCE), **5** and **7** provided different oxidation reactions.
(11) Several unknown by-products were observed. Upon employing acetone as a solvent, anodic oxidation of **7** provided **8** (40%), along with several by-products.
(12) Grieco, P. A.; Gilman, S.; Nishizawa, M. *J. Org. Chem.* **1976**, *41*, 1485.
(13) **Selected Spectroscopic Data. Compound 8:** ^{1}H NMR ($CDCl_3$): δ = 2.01 (3 H, d, *J* = 1.5 Hz), 2.1 (4 H, complex), 4.15 (2 H, t, *J* = 6.6 Hz), 6.67 (1 H, dd, *J* = 3, 1.5 Hz), 7.29 (1 H, d, *J* = 3 Hz).
Compound 11: ^{1}H NMR ($CDCl_3$): δ = 2.00 (2 H, complex), 2.16 (3 H, s), 2.61 (t, *J* = 6.6 Hz), 4.06 (2 H, t, *J* = 5 Hz), 6.82 (1 H, s).
Compound 12: ^{1}H NMR ($CDCl_3$): δ = 2.00 (2 H, complex), 2.20 (3 H, s), 2.69 (2 H, t, *J* = 6.6 Hz), 4.06 (2 H, t, *J* = 5 Hz), 6.59 (1 H, s).
Compound 1: ^{1}H NMR($CDCl_3$): δ = 1.24 (3 H, s), 1.30 (3 H, s), 1.9 (2 H, complex), 2.20 (3 H, s), 3.46 (1 H, m), 3.74 (1 H, dd, *J* = 3.6, 10 Hz), 4.91 (1 H, dd, *J* = 17, 1.5 Hz), 5.11 (1 H, dd, *J* = 10.4, 1.5 Hz), 5.97 (1 H, ddd, *J* = 17, 10.4, 6.4 Hz), 6.49 (1 H, s), 6.66 (1 H, s). The spectroscopy was superimposable to the reported one. Found: *m*/*z* = 248.1428. Calcd for $C_{15}H_{20}O_3$ (M): 248.1412.
Compound 23: ^{1}H NMR($CDCl_3$): δ = 1.26 (3 H, s), 1.31 (3 H, s), 1.65 (1 H, q, *J* = 12 Hz), 2.01 (1 H, br dd. *J* = 11.7, 12 Hz), 2.19 (3 H, s), 3.48 (1 H, m), 3.80 (1 H, br d, *J* = 17 Hz), 5.20 (1 H, br d, *J* = 10 Hz), 5.24 (1 H, br d, *J* = 17 Hz), 5.68 (1 H, ddd, *J* = 17, 10, 9.8 Hz), 6.60 (1 H, s), 6.64 (1 H, s). Found: *m*/*z* = 248.1416. Calcd for $C_{15}H_{20}O_3$ (M): 248.1412.