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INTRAMOLECULAR REACTION OF ELECTROGENERATED PHENOXY CATIONS WITH AN OLEFIN BEARING AN ELECTRON-RELEASING GROUP AT THE SIDE CHAIN

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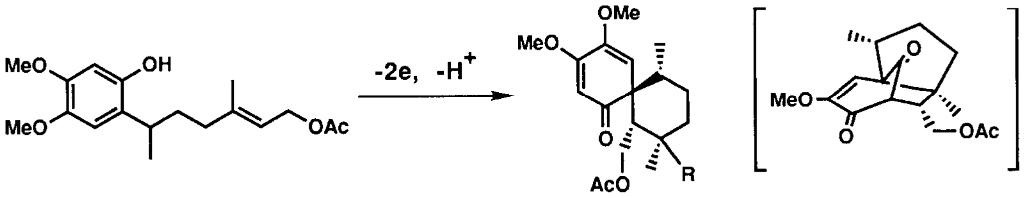
Summary: Some phenols with an olefinic side chain have been electrolyzed under various conditions to afford both intramolecular [5 + 2]cycloaddition products and spiro compounds depending on solvent, substituents on the olefinic double bond and others. These reaction products are regarded as a synthetic key intermediate of bioactive terpenoids.

In connection with our synthetic study on natural products using electrochemical methods as a key step,[1] we further carried out anodic oxidation of 3,4-dimethoxyphenols having different side chains at C_6-position to afford both intramolecular [5 + 2]cycloaddition products and spiro compounds, which may be converted into such bioactive terpenoids as alaskanes,[2] isocomenes,[3] halogenated chamigranes[4] and ingenanes.[5]

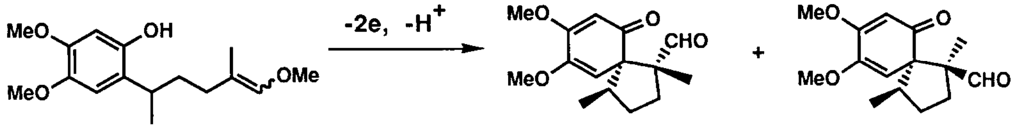
As described in the previous paper,[6] the phenol [A] bearing the trisubstituted olefin at the side chain was subjected to anodic oxidation in acetic anhydride containing $^{n}Bu_4NBF_4$ to give two spiro compounds [**B**: R = OAc, F] (see Scheme 1). However, the corresponding tricyclic compound [C] has not been obtained. This is due to a distribution ratio of electron density belonging to the trisubstituted double bond which is not suitable for intramolecular [5 + 2]cycloaddition leading to the formation of [C].



[A] [B] [C]

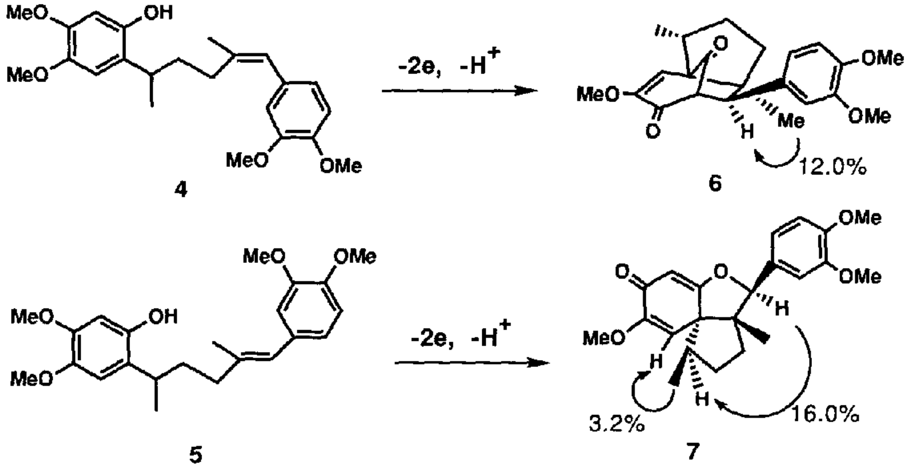
Scheme 1

On the basis of these results, anodic oxidation[7] of the phenol (**1**)[8] having MeO group instead of the acetoxymethyl group in [A] was carried out at constant current [6.9 mA (+700 - 1400 mV *vs*. SCE); 2 F/mol] to afford two spiro compounds (**2** and **3**),[9] in 42 and 22% yields, respectively. However, any intramolecular [5 + 2]cycloaddition product has not been detected.

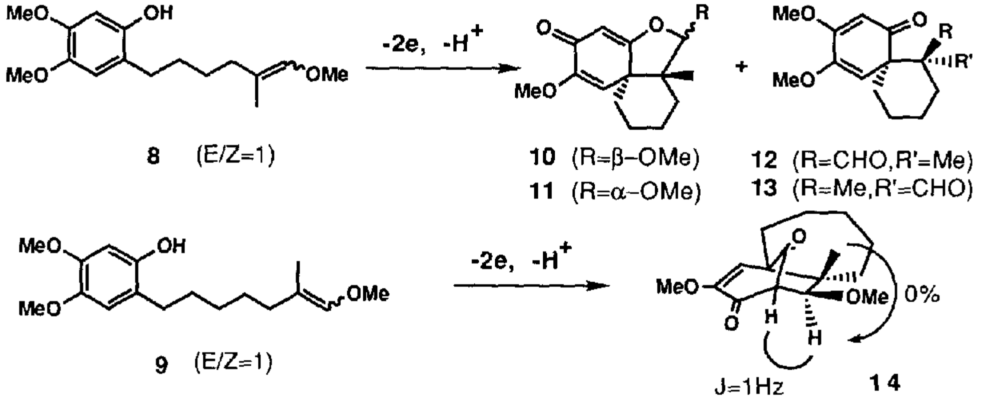


1 (E/Z=1) 2 3

We also carried out anodic oxidation of two geometrical isomers (**4** and **5**)[10] at the side chain, as follows.On electrolysis at constant current [2.1 mA (+800 - 1300 mV *vs.* SCE); 2 F/mol)], the cis isomer (**4**) was selectively converted into the corresponding tricyclic compound (**6**),[9] in 66% yield, from which the isocomenes[3] will be derived. On the other hand, when electrolyzed at constant current [5.9 mA (+730 - 1100mV *vs.* SCE); 2 F/mol)], the trans isomer (**5**) was converted into a spiro compound (**7**)[9] in 69% yield.



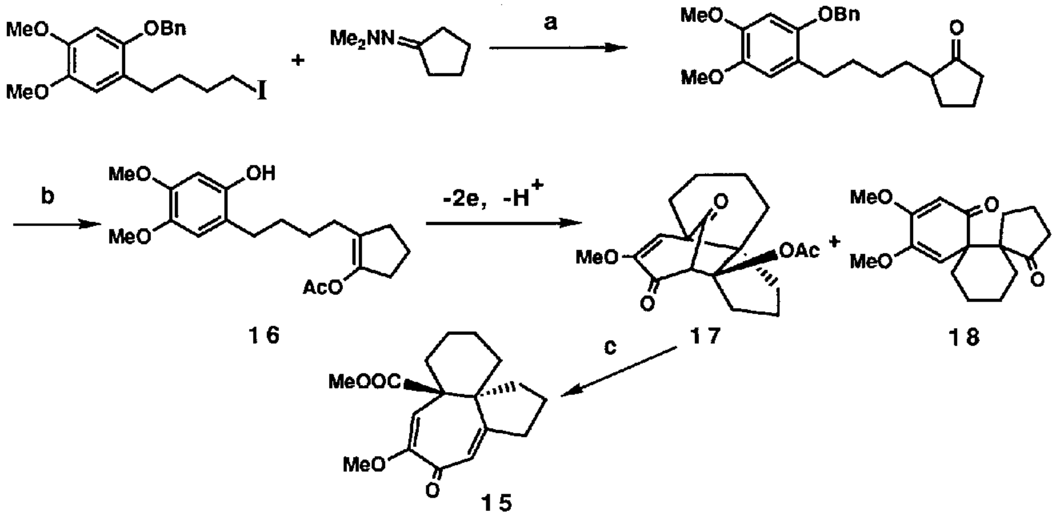
We further examined anodic oxidation of the phenols (**8** and **9**)[8] with a longer side chain. In the case of **8** [CCE at 7.5 mA (+850 - 1250 mV *vs.* SCE); 2 F/mol], four spiro compounds (**10**, **11**, **12** and **13**)[9] were produced in 40, 14, 19 and 11% yields, respectively. Interestingly, on electrolysis of **9** [CCE at 6.2 mA (+740 - 1330 mV *vs.* SCE); 2 F/mol], a tricyclic compound (**14**)[9] was obtained in 19% yield.[11]. Clearly, **14** must be produced from the trans isomer.



From the above results, intramolecular [5 + 2]cycloadditions are primarily influenced by a distribution ratio of electron density at the trisubstituted double bond: in contrast to the phenol [A],[6] indeed, the phenols (**4** and **9**) were electrolyzed to afford the corresponding bicyclo[3.2.1]octanones (**6** and **14**), respectively. In addition, the present study also indicated that steric repulsions and ring strains both make a transition state of the intramolecular [5 + 2] cycloaddition in **1**, **5** and **8** unfavorable, resulting in the formation of spiro compounds in contrast to the phenols (**4** and **9**).

In connection with ingenol,[5] a toxic diterpene, we synthesized a model compound (**15**) using electrochemical method as a key step, as shown in Scheme 2. Namely, the enol acetate (**16**)[12] was subjected to anodic oxidation [CCE at 10 mA (+700 - 900 mV *vs.* SCE); 2 F/mol] using acetic anhydride containing $^nBu_4NBF_4$ to afford a tetracyclic compound (**17**)[9] and a spiro compound (**18**)[9] in 33 and 42% yields, respectively, wherein a platinum net was used instead of a glassy carbon beaker as an anode. In the case of AcOH - EtOH (2 : 3), the latter was selectively obtained in 70% yield. Further treatment of **17** with K_2CO_3 in MeOH gave rise to the desired tricyclic compound (**15**)[9] in quantitative yield.

Synthetic studies on isocomenes, chamigranes and ingenanes are further in progress.



a) 1) ^nBuLi / THF (room temp., 3h), 2) 2M HCl (room temp., 13.5h) (94% overall yield); b) 1) H_2 / Pd-C / MeOH (room temp., 1h) (93%), 2) $^tBuMe_2SiCl$ / imidazole / DMF (room temp., 35.5h) (100%), 3) Ac_2O / CSA (refluxing temp., 42.5h) (100%), 4) $^nBu_4NF$ / THF (0°C, 1h) (100%); c) K_2CO_3 / MeOH (room temp., 30min.)

Scheme 2

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7. A glassy carbon beaker and a platinum wire tip were used as an anode and a cathode, respectively. Acetic

anhydride was also used as the solvent including ^{n}Bu$_4$NBF$_4$ as a supporting electrolyte

8. All new compounds described herein gave satisfactory spectral data consistent with the assigned structures. Particularly, an inseparable 1 : 1 mixture of trans and cis isomers at the side chain is confirmed by the ^{1}H NMR spectrum. **1**: δ (CDCl3) 1.53(3/2H,s), 1.54(3/2H, s) and 3.53(3H, s). **8**: δ (CDCl$_3$) 1.48(3/2H, d, J = 1.3 Hz), 1.56(3/2H, d, J = 1.3 Hz), 3.52(3/2H, s) and 3.55(3/2H, s). **9**: δ (CDCl$_3$) 1.48(3/2H, d, J = 1.3 Hz), 1.56(3/2H, d, J = 1.3 Hz), 3.50(3/2H, s), and 3.52(3/2H, s).

9. The spectral data for the new compounds are in accord with the structures assigned. Particularly, their stereostructures are based on NOE experiments and only selected data are cited: **2** as an oil: $C_{15}H_{20}O_4$ [m/z 264.1380 (M$^+$)]; IR (film) 1720 and 1630 cm^{-1}; δ (CDCl$_3$) 0.83(3H, d, J = 6.6 Hz), 1.00(3H, s), 2.85(1H, m), 3.83(3H, s), 5.06(1H, s), 5.52(1H, s) and 9.73(1H, s). **3** as an oil: $C_{15}H_{20}O_4$ [m/z 264.1358 (M$^+$)]; IR (film) 1720 and 1630 cm^{-1}; δ (CDCl$_3$) 0.76(3H, d, J = 7.0 Hz), 1.14(3H, s), 3.00(1H, m), 3.68(3H, s), 3.81(3H, s), 5.08(1H, s), 5.57(1H, s) and 9.20(1H, s). **6** as an oil: $C_{22}H_{26}O_5$ [m/z 370.1779 (M$^+$)]; IR (film) 1760 and 1700 cm^{-1}; δ (CDCl$_3$) 0.87(3H, d, J = 6.8 Hz), 1.27(3H, s), 1.76(1H, m), 2.72(1H, m), 3.51(2H, s), 3.83(3H, s), 3.88(3H, s), 3.89(3H, s), 6.20(1H, s), 6.70(1H, d, J = 1.8 Hz), 6.82(1H, dd, J = 8.3, 1.8 Hz) and 6.86(1H, d, J = 8.3 Hz). **7** as an oil: $C_{22}H_{26}O_5$ [m/z 370.1797 (M$^+$)]; IR (film) 1650 and 1610 cm^{-1}; δ (CDCl$_3$) 0.59(3H, s), 0.85(3H, d, J = 6.8 Hz), 2.30(1H, m), 2.43(1H, m), 3.70(3H, s), 3.89(6H, s), 5.31(1H, s), 5.61(1H, s), 5.86(1H, s), 6.76(1H, d, J = 2.0 Hz), 6.82(1H, dd, J = 8.3, 2.0 Hz) and 6.86(1H, d, J = 8.3 Hz). **10** as a white solid: $C_{15}H_{20}O_4$ [m/z 264.1381 (M$^+$)]; IR (film) 1650, 1630 and 1610 cm^{-1}; δ (CDCl$_3$) 0.77(3H, s), 3.64(3H, s), 3.69(3H, s), 5.67(1H, s), 5.68(1H, s) and 5.71(1H, s). **11** as a white solid: $C_{15}H_{20}O_4$ [m/z 264.1345 (M$^+$)]; IR (film) 1655, 1640 and 1610 cm^{-1}; δ (CDCl$_3$) 0.86(3H, s), 3.54(3H, s), 3.69(3H, s), 5.06(1H, s), 5.67(1H, s) and 5.81(1H, s). **12** as an oil: IR (film) 1715 and 1625 cm^{-1}); δ (CDCl$_3$) 0.83(3H, s), 1.20 - 2.40(8H, complex), 3.76(3H, s), 3.83(3H, s), 5.45(1H, s), 5.64(1H, s) and 10.39(1H, s). **13** as an oil: IR (film) 1720 and 1630 cm^{-1}; δ (CDCl$_3$) 1.11(3H, s), 1.20 - 2.40(8H, complex), 3.69(3H, s), 3.80(3H, s), 5.47(1H, s), 5.62(1H, s) and 9.31(1H, s). The molecular ion peak has not been observed in mass spectra of both **12** and **13**, but their structures are supported by the above spectral data. **14** as an oil: $C_{16}H_{22}O_4$ [m/z278.1512 (M$^+$)]; IR (film) 1765 and 1690 cm^{-1}; δ (CDCl$_3$) 0.99(3H, s), 3.25(1H, d, J = 1.0 Hz), 3.36(3H, s), 3.52(1H, d, J = 1.0 Hz), 3.71(3H, s) and 6.00(1H, s). **15** as an oil: $C_{17}H_{22}O_4$ [m/z 290.1521 (M$^+$)]; IR (film) 1725, 1660 and 1620 cm^{-1}; δ (CDCl$_3$) 3.63(3H, s), 3.66(3H, s), 5.06(1H, s) 6.08(1H, dd, J = 2.0, 1.5 Hz).**17**: mp 190 - 191 ^{o}C; $C_{18}H_{22}O_5$ [m/z 318.1457 (M$^+$)]; IR (CDCl$_3$) 1760, 1750, 1695 and 1605 cm^{-1}; δ (CDCl$_3$) 3.63(3H, s), 3.79(3H, s), 5.13(1H, s) and 5.33(1H, s).

10. Both cis and trans isomers (**4** and **5**) were synthesized from 3,4-dimethoxyphenol in 8 and 23% overall yields, respectively [1) crotyl chloride/K$_2$CO$_3$ (94%); 2) 200 ^{o}C, 3 h; 3) BnCl/K$_2$CO$_3$ (96% in 2 steps); 4) BH$_3$Me$_2$S and then 35%H$_2$O$_2$/3M NaOH (93%); 5) Me$_2$SO/DCC/pyridine/CF$_3$COOH (100%); 6) Ph$_3$P=CH(OMe)/toluene and then p-TsOH/H$_2$O-acetone (88%); 7) MeLi/ether; 8) DMSO/DCC/pyridine /CF$_3$COOH; 9) H$_2$/Pd-C/EtOAc; 10) ^{t}BuMe$_2$SiCl/imidazole/DMF (76% in 4 steps); 11) NaBH$_4$/dioxane; 12) MsCl/pyridine/CH$_2$Cl$_2$; 13) NaI/acetone (85% in 3 steps); 14) 3,4-dimethoxybenzaldehyde dithiane/^{n}BuLi /THF-hexane; 15) HgO/HgCl$_2$/80% aq.acetone; 16) NaBH$_4$/dioxane-MeOH; 17) ^{n}Bu$_4$NF/THF; 18) Ac$_2$O /pyridine/toluene; 19) CSA/toluene (77% in 6 steps); 20) K$_2$CO$_3$/MeOH (100%; **4/5** = 1/3)]. **4** as an oil: $C_{23}H_{30}O_5$ [m/z 386.2080 (M$^+$)]; IR (film) 3450 cm^{-1}; δ (CDCl$_3$) 1.22(3H, d, J = 6.8 Hz), 1.73 - 1.81(2H, complex), 1.85(3H, d, J = 1.5 Hz), 2.17 - 2.23(2H, complex), 2.25(1H, m), 3.81(6H, s), 3.83(3H, s), 3.87(3H, s), 4.38(1H, br.s, OH), 6.19(1H, br.s), 6.34(1H, s), 6.61(1H, dd, J = 8.3, 1.5 Hz), 6.65(1H, s), 6.68(1H, d, J = 1.5 Hz) and 6.72(1H, d, J = 8.3 Hz). **5** as an oil: $C_{23}H_{30}O_5$ [m/z 386.2080 (M$^+$)]; IR (film) 3450 cm^{-1}; δ (CDCl$_3$) 1.27(3H, d, J = 6.6 Hz), 1.70 - 1.92(2H, complex), 1.84(3H, d, J = 1.0 Hz), 2.04 - 2.12(2H, complex), 3.00(1H, m) 3.83(3H, s), 3.87(9H, s), 4.50(1H, br.s, OH), 6.17(1H, br.s), 6.41(1H, s), 6.69(1H, s) and 6.71 - 6.81(3H, complex). The structures of these geometrical isomers were determined by NOE experiments.

11. Isolated from the reaction mixture which showed several spots on an analytical TLC plate [Kieselgel F$_{254}$; hexane - EtOAc (2 : 1)].

12 **16** as a pale yellow oil: $C_{19}H_{26}O_5$ [m/z 334 (M$^+$)]*; IR (film) 3450 and 1760 cm^{-1}; δ (CDCl$_3$) 1.30 - 1.60(6H, complex), 1.70 - 2.52(8H, complex), 2.06(3H, s), 3.72(6H, s), 4.64(1H, br.s, OH), 6.32(1H, s) and 6.51(1H, s). * The molecular ion peak has not been detected in high resolution mass spectrum.

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