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Intramolecular Reaction of Electrogenerated Phenoxy Cations with an Olefinic Side Chain

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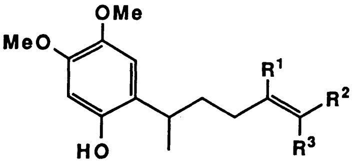
Some phenols with an olefinic double bond at the side chain have been subjected to anodic oxidation under various conditions to afford tricyclo[5.3.1.$0^{1,5}$]undec-9-en-8,11-diones and two different spiro compounds, precursors of bioactive natural products.

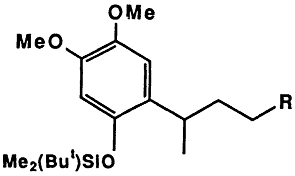
In connection with our synthetic study on bioactive natural products using electrochemical methods as a key step, both helminthosporal$^{1)}$ and 8,14-cedranoxide$^{2)}$ have been synthesized as a racemic form. We further examined anodic oxidation of 3,4-dimethoxyphenols (1 - 4), bearing different side chains at C_6-position, resulting in the formation of tricyclo[5.3.1.$0^{1,5}$]undec-9-en-8,11-diones and two different spiro compounds, from which a number of sesquiterpenes such as silphinenes,$^{3)}$ alaskanes$^{4)}$ and halogenated chamigranes$^{5)}$ may be derived. Initially, the four phenolic compounds (1 - 4) were synthesized as substrates for anodic oxidation.

The known aldehyde (5)$^{2)}$ was readily converted into the desired trisubstituted olefin (1)$^{6)}$ in 2 steps [1) $Ph_3P=CMe_2$/THF under argon (room temp, 2 h) (87%); 2) Bu^n_4NF/THF (room temp, 20 min) (97%)]. The disubstituted olefin (2)$^{6)}$ was synthesized from 5 in 4 steps [1) $(EtO)_2P(O)CH_2COOEt$, NaH/THF under argon (room temp, 12 h) (98%); 2) DIBAL-H/THF under argon (-78 °C, 25 min) (90%); 3) Ac_2O/pyridine (room temp, 15 h) (100%); 4) Bu^n_4NF/THF (room temp, 15 min) (82%)]. According to essentially the same procedure as described in 2, the methyl ketone (6)$^{6)}$ derived from the known alcohol (7) was converted into another trisubstituted olefin (3)$^{6)}$ in good yield. The tetrasubstituted one (4)$^{6)}$ was also obtained from 6 in 2 steps [1) $Ph_3P=CMe_2$/toluene under argon (45 °C, 16 h) (70%); 2) 10% Pd-C, $HCOONH_4$/DMF (room temp, 5 h) (86%)]. These four phenols (1 - 4) were subjected to anodic oxidation using a 30 ml glassy carbon beaker and a platinum wire tip as an anode and a cathode, respectively.

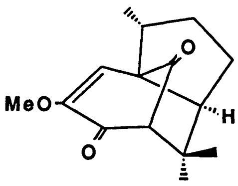
When electrolyzed at a constant current [58 mA (+920 - 1700 mV vs. SCE); ca. 2 F/mol]$^{7)}$ in acetic anhydride containing $Bu^n_4NBF_4$ as a supporting electrolyte, the phenol (1) was converted into 2,6,6-trimethyl-9-methoxytricyclo]5.3.1.$0^{1,5}$]undec-9-en-8,11-dione (8)$^{8)}$ and a spiro compound (9),$^{8)}$ in 54 and 26% yields, respectively, whose stereostructures were determined on the basis of their ^1H NMR



1 R^1 = H, R^2 = R^3 = Me
2 R^1 = R^3 = H, R^2 = CH_2OAc
3 R^1 = Me, R^2 = CH_2OAc, R^3 = H
4 R^1 = R^2 = R^3 = Me



5 R = CHO
6 R = COMe
7 R = OH



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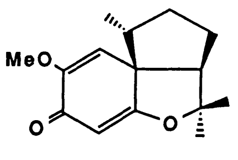
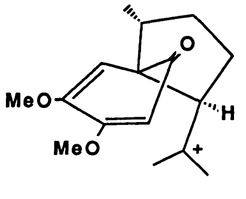
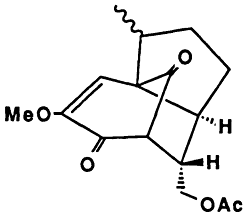


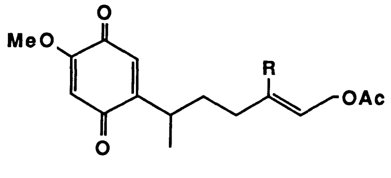
9



[A]



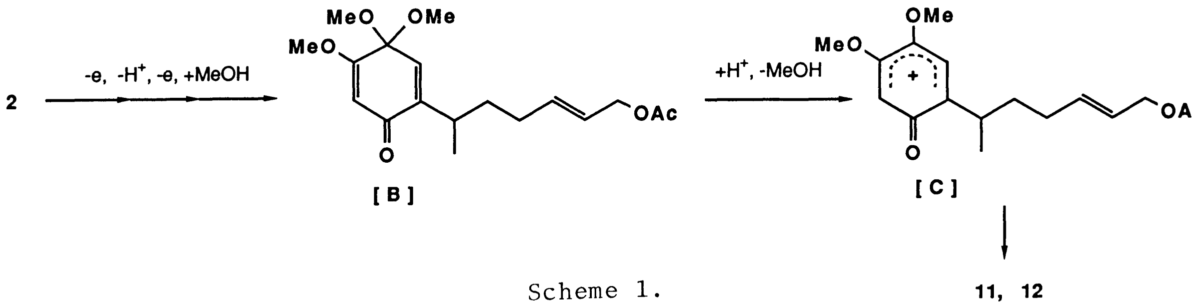
11 α-sec. Me
12 β-sec. Me



10 R = H
15 R = Me

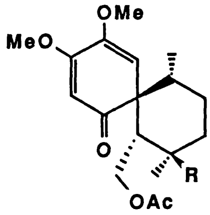
spectra with aid of decoupling and NOE experiments. The spiro compound (9) related to alaskanes is presumably formed from a plausible intermediate [A]. In this case, the stereoisomer of 8 has not yet been found.

Under essentially the same condition as described above, the anodic oxidation of the phenol (2) with a disubstituted double bond was carried out using acetic anhydride as solvent to afford only a quinone (10)[6] instead of the desired tricyclic compound (11). Probably, intramolecular cycloaddition of the electrogenerated phenoxy cation in 2 requires more vigorous conditions as compared with that in 1, because of weak electron donation of the disubstituted double bond in the former. After all, a solution of 2 in MeOH - AcOH (3 : 2) was electrolyzed at a constant current [2.0 mA (+560 - 1000 mV *vs*. SCE); *ca*. 2 F/mol] using $LiClO_4$ as a supporting electrolyte, and then diluted with toluene and concentrated under reduced pressure at 100 °C to afford two 6-acetoxymethyl-2-methyl-9-methoxytricyclo[5.3.1.$0^{1,5}$]undec-9-en-8,11-diones [11 (α-Me-C_2); 12 (β-Me-C_2)], in 60% yield (11/12 = 3),[8] whose stereochemistry was based on an exhaustive comparison of ^{1}H NMR spectra between them [δ1.15 (3H, d, J = 7 Hz) in 11; δ1.42 (3H, d, J = 7 Hz) in 12].[9] On electrolysis of 2 using MeOH - AcOH (3 : 2), a dienone [B] must be formed and then on heating converted into tricyclic compounds

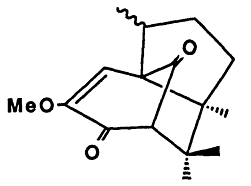


Scheme 1.

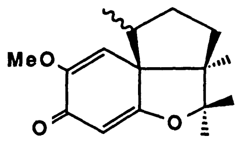
(11 and 12) through a plausible cation [C], as shown in Scheme 1.



13 R = OAc
14 R = F

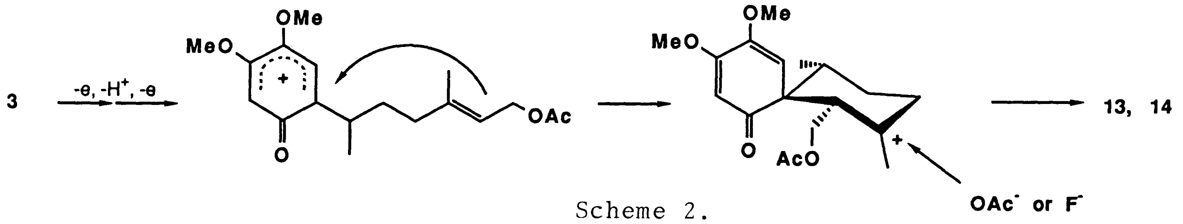


16 α-sec. Me
17 β-sec. Me



18 α-sec. Me
19 β-sec. Me

On anodic oxidation of 3 at a constant current [5 mA (+840 - 1300 mV *vs*. SCE); *ca*. 2 F/mol] using acetic anhydride containing $Bu^n_4NBF_4$, in contrast to 1, any tricyclic compound has not been found, but instead two spiro compounds (13 and 14)[8] related to chamigranes were obtained in 19 and 15% yields, respectively, in addition to the corresponding quinone (15).[6] Their stereostructures were based on their ^1H NMR spectra with aid of NOE experiments. Presumably, a distribution ratio of electron density belonging to the trisubstituted double bond is not suitable for intramolecular [4 + 2]-cycloaddition leading to such a tricyclic compound as 8, but the spiro compounds (13 and 14) are easily formed, as shown in Scheme 2.



Scheme 2.

Finally, when electrolyzed at a constant current [5.5 mA (+880 - 1300 mV *vs*. SCE); *ca*. 2 F/mol] in acetic anhydride containing $Bu^n_4NBF_4$ as a supporting electrolyte, the phenol (4) with a tetrasubstituted double bond was converted into two tricyclic compounds (16 and 17) and two spiro compounds (18 and 19) [16 + 17: 42% (16/17 = 2); 18 + 19: 19% (18/19 = 1)],[10] the stereostructures of which were unambiguously determined by their spectral data, particularly IR and ^1H NMR spectra.[8] This result is quite similar to that of 1 except for the following point. In addition to the two products (16 and 18) with an α-sec.Me group, the corresponding stereoisomers (17 and 19) with a β-sec.Me group have been obtained on anodic oxidation of 4, because of some steric interaction between the α-sec.Me group and the angular Me group. On the other hand, only two cyclic compounds (8 and 9) with an α-sec.Me group have been found in the case of 1. Further synthetic study on bioactive sesquiterpenes is in progress.

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References

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6) All new compounds described herein gave satisfactory spectral data consistent with the assigned structures.

7) In this case, a 200 ml glassy carbon beaker was used as an anode.

8) The spectral data for the new compounds are in accord with the structures assigned, and only selected data are cited: **8**: $C_{15}H_{20}O_3$ [m/z 248.1414(M$^+$)]; IR (film) 1750, 1680, 1650 cm^{-1}; δ(CDCl$_3$) 1.04(3H, s), 1.09(3H, s), 1.16 (3H, d, J= 7 Hz), 1.40-1.54(2H, complex), 1.77(1H, m), 1.92(1H, m), 2.16(1H, t, J= 8 Hz), 2.66(1H, m), 3.30(1H, s), 3.70(3H, s), 6.43(1H, s). **9**: $C_{15}H_{20}O_3$ [m/z 248.1427(M$^+$)]; IR (film) 1650, 1610 cm^{-1}; δ(CDCl$_3$) 0.77(3H, d, J= 6 Hz), 1.38(3H, s), 1.47(3H, s), 1.60(1H, m), 2.00(1H, m), 2.10-2.20(2H, complex), 2.32(1H, m), 2.60(1H, dd, J= 2, 8 Hz), 3.68(3H, s), 5.41(1H, s), 5.64(1H, s). **11**: $C_{16}H_{20}O_5$ [m/z 292.1309(M$^+$)]; IR (film) 1760, 1750, 1690, 1650 cm^{-1}; δ (CDCl$_3$) 1.15(3H, d, J= 7 Hz), 1.33(1H, m), 1.51(1H, m), 1.96(1H, m), 2.02(3H, s), 2.11(1H, m), 2.20(1H, m), 2.38(1H, m), 2.73(1H, m), 3.70(3H, s), 3.79(1H, d, J= 6 Hz), 4.05(2H, m), 6.38(1H, s). **12**: IR (film) 1760, 1690, 1650 cm^{-1}; δ (CDCl$_3$) 1.35-1.60(2H, complex), 1.42(3H, d, J= 7 Hz), 1.86-2.44(3H, complex), 2.02(3H, s), 2.70(1H, m), 3.56(1H, d, J= 6 Hz), 3.70(3H, s), 4.02(2H, m), 6.23(1H, s). **13**: $C_{20}H_{28}O_7$ [m/z 380.1851(M$^+$)]; IR (film) 1730, 1650, 1630, 1580 cm^{-1}; δ (CDCl$_3$) 0.69(3H, d, J= 7 Hz), 1.42(1H, m), 1.60(1H, m), 1.92(3H, s), 2.00(1H, m), 2.05(3H, s), 2.40(1H, dd, J= 1.4, 1.3 Hz), 2.95(1H, m), 3.69(1H, dd, J= 10, 1.3 Hz), 3.74(3H, s), 3.81(3H, s), 4.35(1H, dd, J= 10. 1.4 Hz), 5.59(1H, s), 5.62(1H, s). **14**: $C_{18}H_{25}FO_5$ [m/z 340.1684(M$^+$)]; IR (film) 1740, 1650, 1620, 1580 cm^{-1}; δ (CDCl$_3$) 0.70(3H, d, J= 6 Hz), 1.43(3H, d, J= 21 Hz), 1.60-1.85(2H, complex), 1.94(3H, s), 2.00(2H, complex), 2.48 (1H, dt, J= 34, 5.6 Hz), 3.64(1H, dd, J= 12, 5.6 Hz), 3.72(3H, s), 3.81(3H, s), 4.34(1H, dd, J= 12, 5.6 Hz), 5.58(1H, s), 5.64(1H, s). **16**: $C_{16}H_{22}O_3$ [m/z 262.1581(M$^+$)]; IR (film) 1760, 1690, 1600 cm^{-1}; δ (CDCl$_3$) 0.99(3H, s), 1.00(3H, s), 1.11(3H, s), 1.17(3H, d, J= 7.8 Hz), 1.40-1.65(3H, complex), 2.10(1H, m), 2.86(1H, m), 3.28(1H, s), 3.73(3H, s), 6.17(1H, s). **17**: IR (film) 1760, 1690, 1600 cm^{-1}; δ(CDCl$_3$) 0.92(3H, s), 1.00(3H, s), 1.13(3H, s), 1.38(3H, d, J= 7.8 Hz), 1.40-2.40(4H, complex), 2.86(1H, m), 3.12(1H, s), 3.73(3H, s), 5.93(1H, s). An inseparable mixture of **18** and **19**: $C_{16}H_{22}O_3$ [m/z 262.1575(M$^+$)]; IR (film) 1645, 1610 cm^{-1}; δ (CDCl$_3$) 0.69(3H, d, J= 6.4 Hz), 0.78(3H, d, J= 6.8 Hz), 0.89(3H, s), 1.05(3H, s), 1.17(3H, s), 1.29(3H, s), 1.32(3H, s), 1.30(3H, complex), 1.56(3H, s), 1.60-2.25(6H, complex), 2.60 (1H, m), 3.67(3H, s), 3.69(3H, s), 5.19(1H, s), 5.30(1H, s), 5.64(1H, s), 5.73(1H, s).

9) The quinone (**10**) was also obtained in 24% yield.

10) The corresponding quinone was obtained in 19% yield.

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