Table I. Palladium-Catalyzed Triethylammonium Formate Reductions of Dinitroaromatic Compounds

compd reduced	conditions (solvent)	product (% yield)	mp, °C (lit. mp, °C)
$1,3\text{-}(O_2N)_2C_6H_4$	1 h, 100 °C	$3\text{-}O_2NC_6H_4NH_2$ (77)	113–114 (114)[a]
$2,4\text{-}(O_2N)_2C_6H_3CH_3$	1 h, 100 °C	$2\text{-}O_2N\text{-}4\text{-}H_2NC_6H_3CH_3$ (92)	77–78 (78–79)[b]
$2,6\text{-}(O_2N)_2C_6H_3CH_3$	20 min, 100 °C	$2\text{-}O_2N\text{-}6\text{-}H_2NC_6H_3CH_3$ (76)	87–88 (91.5)[c]
$3,4\text{-}(O_2N)_2C_6H_3CH_3$	1 h, 100 °C	$4\text{-}O_2N\text{-}3\text{-}H_2NC_6H_3CH_3$ (55)	109–110 (109)[d]
$3,5\text{-}(O_2N)_2C_6H_3CO_2CH_3$	1 h, 100 °C	$3\text{-}O_2N\text{-}5\text{-}H_2NC_6H_3CO_2CH_3$ (65)	159–160 (160)[e]
$2,2'\text{-}(O_2NC_6H_4)_2$	1 h, 100 °C	$2\text{-}H_2NC_6H_4C_6H_4NO_2\text{-}2'$ (75)	64–65 (64.0–64.5)[f]
$2,4\text{-}(O_2N)_2C_6H_3OH$	5 min, reflux (CH_3CN)	$2\text{-}H_2N\text{-}4\text{-}O_2NC_6H_3OH$ (57)	141–142 (142–143)[g]
$2,4\text{-}(O_2N)_2C_6H_3OCH_3$	5 min, reflux (CH_3CN)	$2\text{-}H_2N\text{-}4\text{-}O_2NC_6H_3OCH_3$ (24)	117.0–117.5 (118)[h]
$2,4\text{-}(O_2N)_2C_6H_3NH_2$	10 min, reflux (CH_3CN)	$1,2\text{-}(H_2N)_2\text{-}4\text{-}O_2NC_6H_3$ (49)	198–199 (198)[i]
$2,4\text{-}(O_2N)_2C_6H_3NHCOCH_3$	5 min, reflux (CH_3CN)	$2\text{-}H_2N\text{-}4\text{-}O_2NC_6H_3NHCOCH_3$ (56)	204–205 (205)[j]

[a] A. W. Hofmann and J. S. Muspratt, *Ann. Chim. (Paris)*, **57**, 219 (1845). [b] E. Noelting and A. Collin, *Chem. Ber.*, **17**, 263 (1884). [c] E. Noelting, *ibid.*, **37**, 1024 (1904). [d] J. Kenner and M. Parkin, *J. Chem. Soc.*, 858 (1920). [e] A. Herre, *Chem. Ber.*, **28**, 596 (1895). [f] G. M. Badger and W. F. H. Sasse, *J. Chem. Soc.*, 4 (1957). [g] K. Auwers and H. Röhrig, *Chem. Ber.*, **30**, 995 (1897). [h] R. Meldona, G. H. Woolcott, and E. W. Ray, *J. Chem. Soc.*, **69**, 1330 (1896). [i] E. Heim, *Chem. Ber.*, **21**, 2305 (1888). [j] M. A. Phillips, *J. Chem. Soc.*, 1409 (1930).

only 24% monoamine. We could not isolate pure reduction products from 2,4-dinitrophenyl acetate or from 2,4,6-trinitrotoluene. The triethylammonium formate reductions reduce the least hindered nitro group in 2,4-dinitrotoluene (the 4-nitro group) but the more hindered, ortho, nitro group in 2,4-dinitrophenol, 2,4-dinitroanisole, 2,4-dinotroaniline, and 2,4-dinitroacetanilide. Thus, the formate reductions parallel the sulfide and not the stannous chloride reductions of dinitro compounds.

The triethylammonium formate reductions proceed in yields comparable to those reported for sulfide reductions. The formate reductions are more convenient to work up and the use of toxic hydrogen sulfide or compounds which evolve hydrogen sulfide is avoided.

Experimental Section

Materials. Triethylamine (Aldrich) was stored over Davison 4-Å molecular sieves and otherwise used as received. The 97% formic acid (Aldrich) also was used as received. The 10% palladium on charcoal was a product of Matheson Coleman and Bell. *m*-Dinitrobenzene, 2,4-dinitrotoluene, and 2,4,6-trinitrotoluene were products of the Eastman Kodak Company and the 2,6- and 3,4-dinitrotoluenes were from Aldrich.

2,4-Dinitrophenol, mp 112–113 °C,[4] and 2,4-dinitroanisole, mp 86.5–87.8 °C,[5] were prepared by published procedures. 2,4-Dinitrophenyl acetate, mp 70–71 °C, was obtained by acetylation of the phenol with acetic anhydride. 2,4-Dinitroacetanilide, mp 121–122 °C, was produced by acetylation of 2,4-dinitroaniline (Aldrich) with acetic anhydride. Methyl 3,5-dinitrobenzoate, mp 111–112 °C, was obtained from 3,5-dinitrobenzoyl chloride (Fisher) and methanol.

General Procedure for Selective Reduction of Dinitroaromatics. Compounds without Hydroxyl, Alkoxyl, Ester, Amino, or Acetamido Substituents. In a 50-mL three-necked round-bottomed flask equipped with a reflux condenser and a stirrer was placed 10 mmol of the dinitro compound, 0.11 g of 10% palladium on carbon and 6 mL of triethylamine (45 mmol). The mixture was heated to boiling and while stirring 1.6 mL of 97% formic acid (43 mmol) was added dropwise over a period of a few minutes. The mixture was then boiled for 20 min to 1 h. The progress of the reduction was followed by TLC on alumina with chloroform as the eluant. Reactions were terminated after disappearance of the starting material. After the reaction mixture was cooled, methylene chloride was added and the catalyst was removed by filtration. The solvent and excess triethylamine were removed under reduced pressure and the residues were either distilled (*o*-nitroaniline, 2-nitro-4-aminotoluene, and 4-nitro-2-aminoanisole), chromatographed on alumina (4-nitro-3-aminotoluene, methyl 3-nitro-5-aminobenzoate, and 4-nitro-1,2-phenylenediamine), or recrystallized directly (2-nitro-6-aminotoluene, 2-nitro-2'-aminobiphenyl, 4-nitro-2-amino-phenol, and 4-nitro-2-aminoacetanilide).

Compounds with Hydroxyl, Alkoxyl, Ester, Amino, or Acetamido Substituents. The same quantities as in the above procedure were used except that 5 mL of acetonitrile was added initially and the formic acid was added dissolved in 5 additional mL of acetonitrile. The formic acid solution was added dropwise over a period of 15 min to a stirred solution of the dinitro compound, cooled to 15 °C in a cold water bath. After the addition, the mixture was quickly heated to boiling for 5–10 min and then cooled. Products were isolated as in the above procedure.

Acknowledgment is made to the donors of the Petroleum Research Fund, administered by the American Chemical Society, for support of this research.

Registry No. 1,3-Dinitrobenzene, 99-65-0; 2,4-dinitrotoluene, 121-14-2; 2,6-dinitrotoluene, 606-20-2; 3,4-dinitrotoluene, 610-39-9; methyl 3,5-dinitrobenzoate, 2702-58-1; 2,2'-dinitrobiphenyl, 2436-96-6; 2,4-dinitrophenol, 51-28-5; 2,4-dinitroanisole, 119-27-7; 2,4-dinitroaniline, 97-02-9; 2,4-dinitroacetanilide, 610-53-7; *m*-nitroaniline, 99-09-2; 2-nitro-4-aminotoluene, 89-62-3; 2-nitro-6-aminotoluene, 603-83-8; 4-nitro-3-aminotoluene, 578-46-1; methyl 3-nitro-5-aminobenzoate, 23218-93-1; 2-nitro-2'-aminobiphenyl, 35883-86-4; 4-nitro-2-aminophenol, 99-57-0; 4-nitro-2-aminoanisole, 99-59-2; 4-nitro-1,2-phenylenediamine, 99-56-9; 4-nitro-2-aminoacetanilide, 53987-32-9; palladium, 7440-05-3.

(4) J. A. Moore and D. L. Dalrymple, "Experimental Methods in Organic Chemistry", 2nd ed., W. B. Saunders Co., Philadelphia, PA, 1976, p 197.

(5) B. M. Bogoslovski and L. M. Tsil'man, *Org. Chem. Ind.*, **6**, 445 (1939); *Chem. Abstr.*, **34**, 2360 (1940).

Stereochemisty of Ciliarin, Zexbrevin, and Their Relatives[1]

Pratish K. Chowdhury, Ram P. Sharma, and Gopalakrishna Thyagarajan

Regional Research Laboratory, Jorhat 785 006, Assam, India

Werner Herz* and Serengolam V. Govindan

Department of Chemistry, The Florida State University, Tallahassee, Florida 32306

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In connection with our work on the tagitinins we have reported the conversion of tagitinin A (1) to **2a** and **3a**.[2,3]

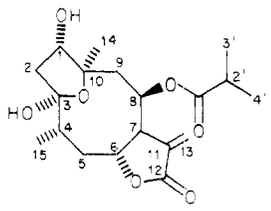
(1) Work at the Florida State University was supported in part by a grant (CA-13121) from the U.S. Public Health Service through the National Cancer Institute.

(2) Baruah, N. C.; Sharma, R. P.; Madhusudanan, K. P.; Thyagarajan, G.; Herz, W.; Murari, R. *J. Org. Chem.* **1979**, *44*, 1831.

(3) To eliminate continuing confusion about how to indicate the correct stereochemistry of these and related heliangolide derivatives, we redraw our earlier formulas in accordance with previously recommended rules[4] so that reentrant angles at tetrahedral ring carbon atoms are shown only when this corresponds to reality. For the 3,10-ethers this results in a change at C-3 (from vertex to reentrant) and for heliangolides in general in a change at C-6 (from reentrant to vertex).

0022-3263/80/1945-4993$01.00/0

Chart I



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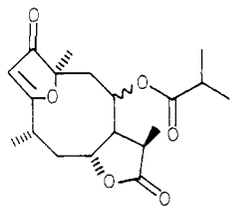
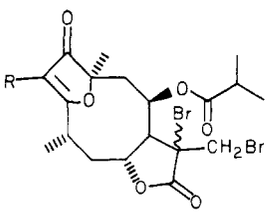
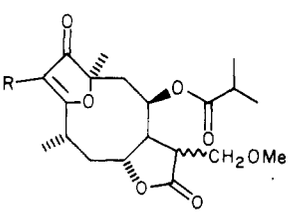


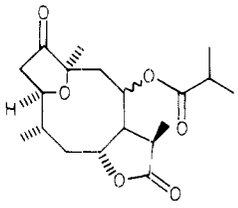
2a, 8-H = α
b, 8-H = β



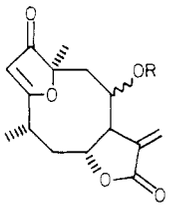
9a, R = H
b, R = Br



10a, R = H
b, R = OH



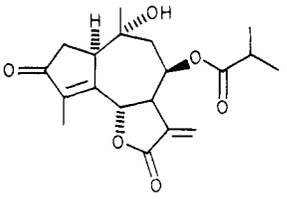
3a, 8-H = α
b, 8-H = β



4a, 8-H = α; R =

b, 8-H = β; R =

c, 8-H = α; R =



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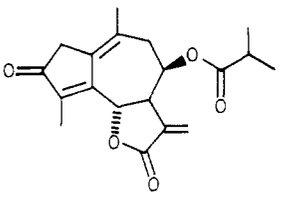

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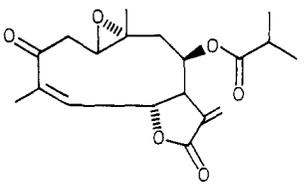

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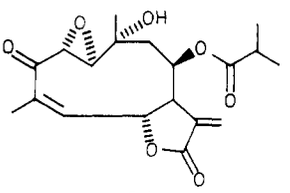

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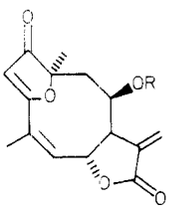
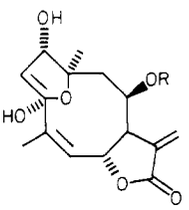


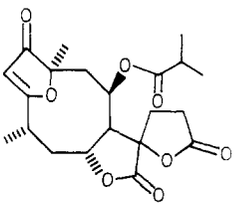
5a, R =

b, R =

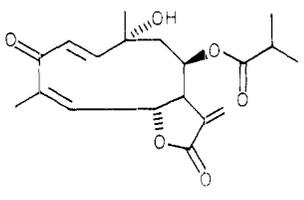


6a, R =

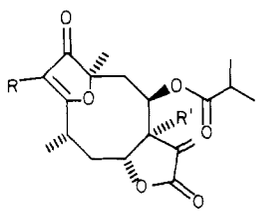
b, R =



15



7



8a, R = H; R′ = OH
b, R = Br; R′ = H
c, R = OH; R′ = H

As the properties of these substances tallied with those reported for tetrahydrozexbrevin and hexahydrozexbrevin for which structures **2b** and **3b** had been derived earlier,[5] we proposed,[2] although authentic samples of these compounds were no longer available, that the C-8 stereochemistry of zexbrevin should be inverted from **4b** to **4a** (see Chart I). If this were so, the same change should also apply to calaxin, ciliarin, zexbrevin B, and orizabin, thus leading to the revised structures **5a,b** and **6ab**, respectively, since all of these have been correlated with zexbrevin.[6] We have now obtained conclusive proof for these reassignments by successful conversions of tagitinin A and tagitinin C (**7**) to ciliarin and orizabin. The reverse transformation of orizabin to tagitinin C has also been accomplished. In addition, we describe some other correlation attempts which while not leading to the desired goal gave products whose formation is of some chemical interest.

Our first effort to effect a correlation between the tagitinins and ciliarin involved oxidation of dehydroanhydrotagitinin A (**4c**) with SeO_2 in dioxane. However, the product was **8a**, not **5b**, as the result of allylic oxidation at C-7. The location of the new hydroxyl was obvious from the ^1H NMR spectrum. The signal of H-7 had disappeared, the characteristic doublets of H-13a and H-13b were now singlets, and the signals of H-6 and H-8 had

(4) Rogers, D.; Moss, G. P.; Neidle, S. *J. Chem. Soc., Chem. Commun.* **1972**, 142.
(5) Romo de Vivar, A.; Guerrero, C.; Diaz, E.; Ortega, A. *Tetrahedron* **1970**, *26*, 1657.
(6) Ortega, A.; Romo de Vivar, A.; Diaz, E.; Romo, J. *Rev. Latinoam. Quim.* **1970**, *1*, 81. Ortega, A.; Guerrero, C.; Romo de Vivar, A.; Romo, J.; Palafox, A. *Ibid.* **1971**, *2*, 38. These substances have been shown[7] to be heliangolides.
(7) Herz, W.; Wahlberg, I. *J. Org. Chem.* **1973**, *38*, 2485.

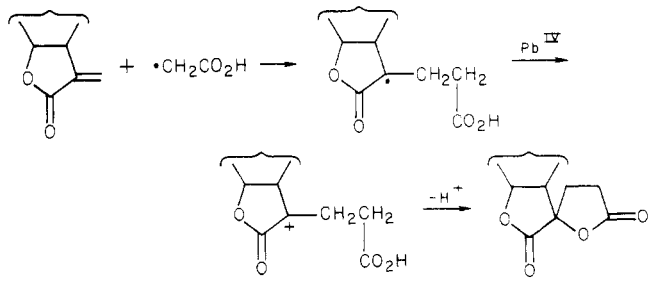
undergone some simplification. Such C-7-hydroxylated sesquiterpene lactones have recently been found to occur naturally,[8a] and our observation suggests a method for their synthesis.

To circumvent C-7 hydroxylation, we decided to protect the C-11,C-13 double bond by addition of bromine. Reaction of **4c** with *N*-bromosuccinimide under ordinary conditions furnished a mixture of **8b**, **9a**, and **9b**, but in the presence of artificial light **9a** was the only product. Debromination of **9a** to **4c** and **9b** to **8b** was accomplished by treatment with zinc in ether, but oxidation of **9a** with SeO_2–acetic acid followed by treatment with Zn furnished again not ciliarin, but the diosphenol **8c**. This reaction may involve oxidation of the hemiketal, produced by hydration of the C-2,C-3 double bond and in equilibrium with the open form. An analogous substance, **10b**, was obtained by hydrolysis (K_2CO_3–MeOH) of **4a** to **10a** and subsequent oxidation with SeO_2. Ciliarin (**5b**) was eventually obtained in 20% yield by oxidation of **4c** with DDQ–TSOH in dioxane. Authentic ciliarin was prepared from orizabin (**6b**) kindly furnished by Dr. Romo de Vivar.[8b]

Acid-catalyzed cyclization of tagitinin C (**7**) gave the guaianolide **11** instead of orizabin as hoped for. The structure of the new compound was evident from the ^1H NMR spectrum in which the low-field H-1, H-2, and H-5 resonances of **7** had been replaced by an ABX system of H-1, H-2a, and H-2b at much higher field and by facile dehydration to a dienone **12** containing two vinyl methyl groups and lacking vinylic hydrogens.[11] Compound **11** was also obtained by acid-catalyzed cyclization of **13**.[2] These reactions are of interest as acid-catalyzed cyclization of *trans,trans*-germacra-1(10),4,5-dienolides[9] and the derived 1(10)-epoxides[10] normally produce eudesmanolides.[13]

On the other hand, reversal of the sequence used for preparation of **13**, i.e., Weitz–Scheffer oxidation of tagitinin C to a mixture of epoxides **14** followed by Zn–acetic acid reduction, gave a mixture of orizabin and its C-1 epimer which was oxidized to ciliarin. Treatment of pure orizabin with sodium acetate–acetic anhydride regenerated tagitinin C in 70% yield.

Scheme I



Reaction of lead tetraacetate did not effect oxidation of **4c** but gave as the major product a substance ($C_{21}H_{26}O_7$) whose formation involved the addition of a CH_2CO_2 unit to the α,β-unsaturated lactone system of **4c**. The ^1H NMR spectrum no longer exhibited the typical narrowly split doublets of H-13a and H-13b near 5.7 and 6.2 ppm, and H-7, now spin coupled only to H-6 and H-8, had experienced a distinct diamagnetic shift to 3.05 ppm. The only structure consonant with the spectrum which contained no new vinyl methyl, $CH_3C(O)$, or CHO resonances was **15**, whose formation is analogous to the synthesis of γ-lactones from olefins and carboxylic acids by reaction with manganic and other higher valence metal carboxylates[14] but involves, for the first time to our knowledge, attack by a carboxy methyl radical on the β-position of an α,β-unsaturated lactone system (Scheme I). The requisite carboxymethyl radical is apparently formed from $Pb(OAc)_4$ indirectly and nonselectively by the usual decarboxylative decomposition of the salt to CO_2 and CH_3 and attack of the latter on solvent acetic acid.[14b]

Experimental Section

Oxidation of 4c. Method a. A mixture of 50 mg of **4c**[2] and 20 mg of SeO_2 in 4 mL of dioxane was refluxed in an oil bath maintained at 120 °C for 1 h, cooled, poured into 200 mL of ice-cold H_2O, and extracted with $CHCl_3$ (4 × 100 mL). The washed and dried extract was evaporated at reduced pressure and the residue purified by preparative TLC (benzene (Bz)–EtOAc, (Bz–EtOAc, 4:1) to give 25 mg of **8a** as a gum: IR 3600, 1760, 1730, 1700, 1600 (vs), 1025, 960, 920 cm^{-1}; NMR ($CDCl_3$, 270 MHz) δ 5.59 (H-2), 3.2 (m, H-4), 2.56 (m) and 2.21 (m, H-5), 4.76 (br d, H-6, $J_{5a,6}$ = 8.5 Hz, $J_{5b,6} \approx$ 1 Hz), 5.33 (dd, H-8, $J_{8,9a}$ = 4.5 Hz, $J_{8,9b}$ = 2.5 Hz), ~2.5 (m, H-9), 6.49 and 6.04 (H-13), 1.45 (H-14), 1.36 (d, H-15, $J_{4,15}$ = 7 Hz), 2.38 (m, H-2′), 1.07 (d) and 1.03 (d, H-3′ and H-4′, J = 7 Hz).

Anal. Calcd for $C_{19}H_{24}O_7$: mol wt 364.1720. Found: mol wt (mass spectroscopy) 364.1724.

Other significant peaks in the high-resolution mass spectrum were found at m/e (composition, relative intensity) 294 ($C_{15}H_{18}O_6$, 26.6), 293 ($C_{15}H_{17}O_6$, 7.8), 276 ($C_{15}H_{16}O_5$, 4.1), 125 ($C_7H_9O_2$, 70.7), 71 (C_4H_7O, 100).

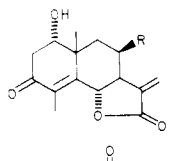
Method b. A mixture of 80 mg of **4c**, 100 mg of DDQ, 120 mg of toluenesulfonic acid, and 5 mL of dioxane was refluxed in an oil bath maintained at 110 °C for 36 h, cooled, and passed through a short column of silica gel (50 g) to remove DDQ and toluenesulfonic acid. Three fractions were collected by using $CHCl_3$, each fraction being 15 mL. Fractions 1 and 2 were combined and further purified on a preparative plate to give 6 mg of ciliarin (**5b**) and 50 mg of unreacted starting material. The product which could not be crystallized because of the small sample exhibited the following: IR 1760, 1730, 1705, 1595, 1140, 1000 cm^{-1}; NMR (270 MHz) δ 5.61 (H-2), 5.94 (dq, H-5, $J_{5,6}$ = 3.5 Hz, $J_{5,15}$ = 1 Hz), 5.34 (tq, H-6, $J_{6,7}$ = 3.5 Hz, $J_{6,15}$ = 1 Hz), 3.68 (m, H-7), 5.22 (ddd,

(8) (a) Herz, W.; Govindan, S. V.; J. F. Blount *J. Org. Chem.* **1980**, *45*, 1113. Bohlmann, F.; LeVan, N. *Phytochemistry* **1978**, *17*, 1957. (b) **Note Added in Proof**: Our synthetic ciliarin was identical with an "isobutyroylatripliciolide" reported by Bohlmann [Bohlmann, F.; Mahanta, P. K.; Natu, A. N.; King, R. M.; Robinson, H. *Phytochemistry* **1978**, *17*, 471 (their formula 17)] as a constituent of *Isocarpha atripicifolia*. The corresponding methacryl ester (their formula **16**) in *I. atriplicifolia* is therefore calaxin. We thank Professor Bohlmann for carrying out this comparison.

(9) Kulkarni, G. H.; Kelkar, G. R.; Bhattacharyya, S. C. *Tetrahedron* **1964**, *20*, 2639 and many later examples reported by other authors.

(10) E.g.: Rodriques, A. A. S.; Garcia, M.; Rabi, J. A. *Phytochemistry* **1978**, *17*, 953.

(11) A priori the NMR spectrum of the cyclization product does not exclude the eudesmanolide formula ia, although in that case the chemical shifts of H-1 and H-14 would differ significantly from those reported for ludovicin C (ib),[12] and subsequent formation of **12** would have to involve a molecular rearrangement. However, its resistance to oxidation (Jones reagent) and acetylation (Ac_2O–pyridine, room temperature) and the absence of an IR band in the region 1650–1700 cm^{-1} (ct. a ludovicin C band at 1670 cm^{-1}) rule out this possibility.



ia, R = 

b, R = H

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H-8, $J_{7,8}$ = 2 Hz), 2.51 (dd, H-9a, $J_{8,9a}$ = 6 Hz, $J_{9a,9b}$ = 15 Hz), 2.25 (dd, H-9b, $J_{8,9b}$ = 4 Hz), 6.34 (d, 2.5 Hz) and 5.68 (d, J = 2 Hz, H-13), 1.50 (H-14), 2.09 (br, H-15), 2.45 (m, H-2′), 1.12 (d, J = 7 Hz), 1.11 (d, J = 7 Hz, H-3′ and H-4′); mass spectrum, m/e 346 (M^+), 276, 275, 258, 232, 97, 71. All properties coincided with those of authentic ciliarin prepared from orizabin as follows. A solution of 15 mg of orizabin in 5 mL of AnalaR acetone was cooled to 0 °C and mixed with 6 drops of Jones reagent. After 0.5 h at 0 °C excess reagent was destroyed with MeOH. The mixture was diluted with H_2O and extracted with $CHCl_3$; the washed and dried extract was puridied by preparative TLC (Bz–EtOAc, 4:1) to give 8 mg of ciliarin as a gum which could not be crystallized because of the small quantity available.

Reaction of NBS with 4c. Method a. A mixture of 50 mg of **4c** and 40 mg of *N*-bromosuccinimide in 10 mL of $CHCl_3$ was refluxed for 1 h while being irradiated with light from a 100-W light bulb, cooled, and washed with H_2O. The washings were thoroughly extracted with $CHCl_3$; the combined $CHCl_3$ fractions were dried, evaporated, and purified by preparative TLC (Bz–EtOAc, 3:1) to give 40 mg of **9a** which was recrystallized from EtOAc: mp 174–175 °C; NMR (60 MHz) δ 5.45 (H-2), 5.05 (m, H-8), 4.50 (m, H-6), 4.20 (d) and 3.70 (d, J = 11 Hz, H-13), 1.40 (H-14), 1.25 (d, J = 7 Hz, H-15), 1.10 (d, J = 7 Hz, H-3′ and H-4′); mass spectrum, m/e 510, 508, 506 (M^+), 440, 438, 436 ($M^+ - C_4H_6O$), 341, 339, 314, 312 and 260. A solution of 30 mg of **9a** in 15 mL of ether was stirred at room temperature with 50 mg of Zn dust until TLC indicated complete disappearance of starting material (~1 h). Filtration and evaporation of solvent gave **4c** in quantitative yield.

Method b. Reaction of 50 mg of **4c** with 50 mg of NBS in 10 mL of $CHCl_3$ without illumination followed by the usual workup and preparative TLC gave as the most polar product 10 mg of the monobromo derivative **8b** as a gum: NMR (60 MHz) δ 6.25 (d) and 5.65 (d, J = 3 Hz, H-13), 5.05 (m, H-8), 4.40 (m, H-6), 3.25 (m, H-7), 1.35 (H-14), 1.15 (d, J = 7 Hz, H-15), 1.05 (d, J = 7 Hz, H-3′, H-4′); mass spectrum, m/e 428, 426 (M^+), 359, 358, 357, 356, 277, 259, 231, 71. The middle fraction (15 mg) was **9a**, and the least polar fraction (10 mg) was the tribromo derivative **9b**: mass spectrum, m/e 590, 588, 586, 584 (M^+). Reduction of **9b** (10 mg) with Zn in ether as described under in method a gave 6 mg of monobromide **8b**.

Conversion of 9a to 8c. A mixture of 50 mg of **9a** and 30 mg of SeO_2 in 5 mL of glacial acetic acid and 1 mL of H_2O was refluxed (120 °C) for 2 h at which time TLC indicated that the starting material had disappeared and one major product had been formed. The mixture was diluted with H_2O and extracted with $CHCl_3$. The washed and dried extract was evaporated at reduced pressure; traces of acetic acid were removed by distillation with toluene. The residue was purified by preparative TLC (Bz–EtOAc, 3:1) to give 20 mg of a gum which had IR bands at 1780, 1735, 1720, 1705, 1580, 1120, 1020, and 990 cm^{-1} and was debrominated with Zn in ether containing a little acetic acid in the manner described in the previous section. Filtration and evaporation gave a quantitative yield of **8c** as a gum: IR 1760, 1730, 1715, 1700, 1575, 1130, 1120, 1080, 990 cm^{-1}; NMR (270 MHz) 3.90 (m, H-4), 2.4 (m) and 2.03 (m, H-5), 4.34 (br dd, H-6, $J_{5a,6}$ = 1 Hz, $J_{6,7}$ = 5 Hz), 3.16 (m, H-7), 5.13 (br dd, H-8, $J_{7,8}$ < 1 Hz, $J_{8,9a}$ = 5 Hz, $J_{8,9b}$ = 2 Hz), 2.67 (dd, J = 15, 5 Hz) and 2.22 (d, J = 15, 2 Hz, H-9), 6.35 (d, 3.5 Hz) and 5.55 (d, J = 2.5 Hz, H-13), 1.39 (H-14), 1.27 (d, H-15, $J_{4,15}$ = 7 Hz), 2.47 (m, H-2′), 1.16 (d) and 1.10 (d, J = 7 Hz, H-3′ and H-4′); mass spectrum, m/e 364 (M^+) 347, 277, 259, 71 (base peak).

Conversion of 4c to 10b. A mixture of 40 mg of **4c** in 4 mL of MeOH and 30 mg of K_2CO_3 in 2 mL of H_2O was stirred for 1 h at room temperature, acidified with acetic acid, diluted with H_2O, and extracted with $CHCl_3$. Evaporation of the washed and dried extract gave **10a** as a gum: 40 mg; IR 1770, 1730, 1170, 1600, 1130, 1100 cm^{-1}; NMR (60 Mz) δ 5.45 (H-2), 5.0 (m, H-8), 4.38 (m, H-6), 3.40 (OMe), 1.40 (H-14), 1.25 (d, J = 7 Hz, H-15), 1.10 (d, J = 7 Hz, H-3′ and H-4′); mass spectrum, m/e 380 (M^+), 348 ($M^+ - CH_4O$), 292 ($M^+ - C_4H_8O_2$), 278 ($C_{15}H_{18}O_5$), 260 ($C_{15}H_{16}O_4$), 138, 125 (base peak), 71.

Anal. Calcd for $C_{20}H_{28}O_7$: C, 63.14; H, 7.42. Found: C, 63.44; H, 7.14.

A mixture of 40 mg of the preceding compound and 30 mg of SeO_2 in 4 mL of dioxane was refluxed, the progress of the reaction being monitored by TLC. When all of the starting material had disappeared (7 h), the mixture was cooled, diluted with H_2O, and extracted with $CHCl_3$. The washed and dried extract was evaporated and the residue purified by preparative TLC (Bz–EtOAc, 6:1). The major more polar fraction **10b** was a gum: 15 mg; IR 1775, 1730, 1705, 1600, 1580, 1175, 1140, 1100, 1000 cm^{-1}; NMR (270 MHz) at 3.80 (m, H-4), 2.5 (m) and 2.1 (m, H-5), 4.22 (br dd, H-6, $J_{6,7}$ = 5 Hz, $J_{5,6a}$ = 10 Hz, $J_{5,6a}$ < 1 Hz), 2.70 (m, H-7), 5.04 (br dd, H-8, $J_{7,8}$ < 1 Hz, $J_{8,9a}$ = 4.5 Hz, $J_{8,9b}$ = 2 Hz), 2.54 (dd) and 2.14 (dd, H-9, $J_{9a,9b}$ = 15 Hz), 1.43 (H-14), 1.35 (d, H-15, $J_{4,15}$ = 7 Hz), 2.45 (m, H-2′), 1.19 (d) and 1.16 (d, J = 7 Hz, H-3′ and H-4′); mass spectrum, m/e 396 (M^+), 379, 309, 291, 259, 231, 71 (base peak). The less polar gummy fraction (8 mg) was a mixture by NMR criteria.

Conversion of Tagitinin C and 13 to 11. Method a. A solution of 50 mg of tagitinin C (**7**) in 4 mL of CH_3CN was refluxed with 2 drops of H_2O and 50 mg of $SnCl_2$ for 4 h until the starting material had disappeared, diluted with H_2O, and extracted with $CHCl_3$. Evaporation of the washed and dried extract followed by preparative TLC (Bz–EtOAc, 1:1) gave 40 mg of **11**: IR 3500, 1770, 1730, 1700, 1640, 1130, 1100, 1050, 1000, 950 cm^{-1}; NMR (270 MHz) δ 3.32 (br, $W_{1/3}$ = 12 Hz, H-1?) coupled to 2.59 (2 p, H-2?), 5.42 (br d, H-6, $J_{6,7}$ = 10 Hz, $J_{6,15} \approx$ 1.5 Hz), 3.43 (br d, H-7, $J_{7,8} \approx$ 2 Hz, $J_{7,13a}$ = 3 Hz, $J_{7,13b} \approx$ 2.5 Hz), 5.82 (br, $W_{1/2}$ = 9 Hz, H-8), 2.36 (br d), and 2.10 (br d, H-9, $J_{9a,9b}$ = 12 Hz, $J_{9a} = J_{8,9b} \approx$ 3 Hz), 6.37 (br d) and 5.67 (br, H-13), 1.11 (H-14), 2.00 (br, H-15), 2.53 (septet, H-2′, $J_{2',3'} = J_{2',4'}$ = 7 Hz), 1.16 (d) and 1.14 (d, J = 7 Hz, H-3′ and H-4′).

Anal. Calcd for $C_{19}H_{24}O_6$: mol wt 348.1572. Found: mol wt (mass spectrum) 348.1551.

Other significant peaks in the high-resolution mass spectrum were found at m/e (composition, relative intensity) 278 ($C_{15}H_{18}O_5$, 14.4), 260 ($C_{15}H_{16}O_4$, 12.8), 242 ($C_{15}H_{14}O_3$, 3.6), 71 (C_4H_7O, 71.6).

The same product was obtained by substituting $SnCl_4$ for $SnCl_2$, by refluxing **7** with HCO_2H for 1 h, or by keeping **7** in acetone with several drops of $HClO_4$ at room temperature for 1 h.

A solution of 25 mg of **11** in 50 mL of benzene was refluxed with 50 mg of toluenesulfonic acid for 1 h, cooled, diluted with 200 mL of $CHCl_3$, thoroughly washed with H_2O, and dried. Removal of solvent followed by preparative TLC (Bz–EtOAc, 3:1) gave 15 mg of **12** as a gum: IR 1775, 1725, 1700, 1140, 1070 cm^{-1}; NMR (60 MHz) δ 6.25 (d, J = 3 Hz) and 5.65 (d, J = 2.5 Hz, H-13), 5.50 C (H-6 and H-8), 2.05 (H-15), 2.00 (H-14), 1.10 (d, J = 7 Hz, H-3′ and H-4′); mass spectrum, m/e 330 (M^+), 259 ($M^+ - C_4H_7O$), 242 ($M^+ - C_4H_8O_2$), 71 (C_4H_7O).

Method b. Reaction of 30 mg of **13**[2] with 1 mL of HCO_2H at 100 °C for 1 h followed by the usual workup and preparative TLC gave 25 mg of **11**. Keeping 20 mg of **13** in 4 mL of acetone and 4 drops of $HClO_4$ at room temperature for 1 h gave 15 mg of **11**.

Conversion of Tagitinin C to Orizabin. A solution of 50 mg of tagitinin C in 4 mL of dioxane was cooled to 0 °C and allowed to stand overnight at −5 °C with 0.5 mL of a solution prepared from 5 mL of 30% H_2O_2, 5 mL of H_2O, and 10 mg of Na_2CO_3. Acidification with acetic acid, dilution with H_2O, extraction with $CHCl_3$, evaporation of the washed and dried extract, and preparative TLC (Bz–EtOAc, 4:1) gave 35 mg of a gum which on the basis of the NMR spectrum was a mixture of epoxide isomers **14**: IR 3500, 1770, 1730, 1680, 1150, 1110, 1060, 1000, 900 cm^{-1}; NMR signals of major isomer at 6.35 (d) and 5.95 (d, J = 3 Hz, H-13), 5.57 (m, H-5), 5.5 (m, H-6 and H-8), 3.8–3.2 (H-7, H-1, and H-2), 2.00 (H-15), 1.30 (H-14), 1.10 (d, J = 7 Hz, H-3′ and H-4′); mass spectrum, m/e 364 (M^+), 346, 328, 276, 71.

Anal. Calcd for $C_{19}H_{24}O_7$: C, 62.62; H, 6.64. Found: C, 62.42; H, 6.38.

To a solution of 35 mg of **14** in 4 mL of glacial acetic acid and 1.5 mL of H_2O heated to 100 °C was added in small portions 0.1 g of Zn dust over 30 min with occasional shaking. After 1 h the mixture was cooled, diluted with H_2O, neutralized with $NaHCO_3$, and extracted with $CHCl_3$. Evaporation of the washed and dried extract and purification by preparative TLC (Bz–EtOAc, 2:1) gave 8 mg of a gum: IR 3500, 1760, 1730, 1650, 1175, 1130, 1110, 1060, 980 cm^{-1}; mass spectrum, m/e 366 (M^+), 348, 330, 295, 278, 260, 97, 71. The material was identical on TLC with orizabin and had identical IR and mass spectra; however, the 270-MHz NMR spectrum indicated that it also contained the C-1 epimer. Oxidation of the entire product (8 mg) in 4 mL of acetone at 0 °C

with 4 drops of Jones reagent followed by the usual workup gave 4 mg of ciliarin as a gum which could not be crystallized because of the small amount but whose TLC behavior and IR, mass, and NMR spectra were identical with those of authentic material.

Conversion of Orizabin to Tagitinin C. A mixture of 15 mg of orizabin, 40 mg of anhydrous sodium acetate, and 1 mL of acetic anhydride was heated at 100 °C for 30 min, the reaction being monitored by TLC. Dilution with H_2O, extraction with $CHCl_3$, evaporation of the washed and dried extract, and purification of the residue by preparative TLC (Bz–EtOAc, 2:1) furnished 10 mg of tagitinin C, identical on TLC with authentic material. The IR, NMR, and mass spectra were superimposable.

Reaction of 4c with Lead Tetracetate. A solution of 40 mg of **4c** and 100 mg of $Pb(OAc)_4$ in 1.5 mL of glacial acetic acid was refluxed for 7 h, the reaction being monitored by TLC. After disappearance of the starting material the mixture was cooled, diluted with H_2O, and extracted thoroughly with $CHCl_3$. Evaporation of the washed and dried extract and preparative TLC (Bz–EtOAc, 8:1) gave two fractions. The less polar gummy material (8 mg) was a poorly defined mixture (NMR spectrum); the more polar fraction (15 mg), also noncrystalline, was **15**: IR 1775, 1730, 1705, 1605, 1200, 1130, 1030, 955, 100 cm^{-1}; NMR (270 MHz) δ 5.55 (H-2), 3.16 (m, H-4, $J_{4,5}$ = 7, 11 Hz, $J_{4,15}$ = 6.5 Hz), 2.45 (m) and 2.23 (m, H-5), 4.42 (br dd, H-6, $J_{5,6}$ = 10, 1 Hz, $J_{6,7}$ = 5 Hz), 3.05 (br d H-7, $J_{7,8}$ < 1 Hz), 4.93 (br dd, H-8), 2.66 (dd, $J_{8,9a}$ = 5 Hz, $J_{9a,9b}$ = 15 Hz) and 2.10 (dd, $J_{8,9b}$ = 1.5 Hz, H-9), 2.98 (m), 2.5 (m), 2.3 (m, H-13 and H-2″), 1.43 (H-14), 1.35 (d, H-15, $J_{6,5}$ = 1.0 Hz), 2.95 (m, H-2′), 1.14 (d) and 1.12 (d, J = 7 Hz, H-3′, H-4′).

Anal. Calcd for $C_{21}H_{26}O_8$: mol wt 406.1626. Found: mol wt (mass spectrum) 406.1607.

Other significant peaks in the high-resolution mass spectrum were at m/e (composition, relative intensity) 336 ($C_{17}H_{20}O_7$, 1.1), 318 ($C_{17}H_{18}O_6$, 4.2), 300 ($C_{17}H_{16}O_5$, 5.5), 264 ($C_{15}H_{20}O_4$, 2.6), 258 ($C_{15}H_{14}O_4$, 2.5), 125 ($C_7H_9O_2$, 100), 71 (C_4H_7O, 53.6).

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Registry No. 4c, 69440-09-1; **5b**, 30412-87-4; **6b**, 34367-14-1; **6b** (C-1 epimer), 34367-14-1; **7**, 59979-56-5; **8a**, 75197-64-7; **8b**, 75197-65-8; **8c**, 75197-66-9; **9a**, 75197-67-0; **9b**, 75197-68-1; **10a**, 75197-69-2; **10b**, 75197-70-5; 11, 75197-71-6; **12**, 75197-72-7; **13**, 72301-73-6; **14** (isomer 1), 75197-73-8; 14 (isomer 2), 75247-16-4; **15**, 75197-74-9; propanoic acid, 2-methyl-2,3,3a,4,5,6,7,8,9,11a-decahydro-3-bromo-3-(bromomethyl)-6,10-dimethyl-8-hydroxy-2,7-dioxo-6,9-epoxycyclodeca[*b*]furan-4-yl ester, 75213-89-7.

Base-Catalyzed Oxygenation of *tert*-Butylated Phenols. 4.[1] Mechanism of Base-Catalyzed Ortho Regioselective Dioxygen Incorporation into 4-Aryl-2,6-di-*tert*-butylphenols

Akira Nishinaga,* Tadashi Shimizu, Tomoyuki Fujii, and Teruo Matsuura

Department of Synthetic Chemistry, Faculty of Engineering, Kyoto University, Kyoto, Japan

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Base-catalyzed dioxygen incorporation into 4-alkyl-2,6-di-*tert*-butylphenols has been suggested to involve equilibria among the phenolate (i) and peroxy anions (iii and iv) including a π-complex intermediate (ii, Scheme I).[1] The equilibrium is influenced by the solvent and the substituent R. When the anionic species are not associated with the countercation of bases (in EtOH, DMF), the equilibrium is extremely shifted to iii, accomplishing para regioselectivity.[1,2] By contrast, the oxygenation of 2,4,6-tri-*tert*-butylphenol in a *t*-BuOK/*t*-BuOH system, where the anionic species are associated with the potassium cation, leads to the formation of products resulting exclusively from dioxygen incorporation into the ortho position.[2,3] The ortho regioselective dioxygen incorporation with 2,4,6-tri-*tert*-butylphenol has been shown, however, to involve two distinct steps, formation of iii (R = *t*-Bu) in the first step followed by the exclusive migration of the peroxy group to the ortho position,[1] indicating that the initial attack by O_2 in oxygenation of i takes place always on the para position. The subsequent efficient migration of the peroxy group to the ortho position has been concluded to result from stabilization of iv by chelation (v) of the associated form of peroxy anion.[1]

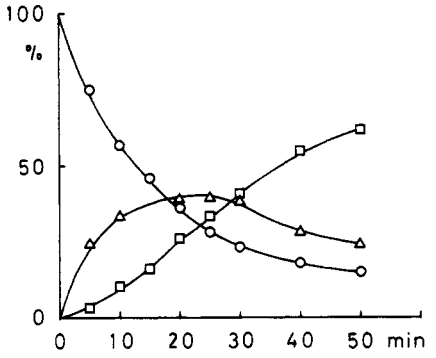
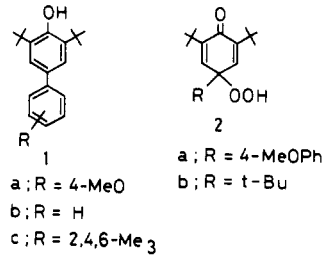


Figure 1. Time course of oxygenation of **1a** in *t*-BuOH–hexane containing *t*-BuOK at −16 °C: [**1a**], 50 mM; ○, **1a**; △, **2a**; □, **3a**.

On the other hand, base-catalyzed oxygenation of 4-aryl-2,6-di-*tert*-butylphenols (**1**) in a *t*-BuOK/*t*-BuOH system where dioxygen is incorporated only into the ortho position, giving rise to the products **3**–**5**, has been postulated to involve direct attack by O_2 on the ortho position.[1,4]

We now find that at −16 °C the oxygenation of 2,6-di-*tert*-butyl-4-(4-methoxyphenyl)phenol (**1a**) also affords the peroxy-*p*-quinolate intermediate of type iii in Scheme I. Such an intermediate has never been detected at higher temperature or after a long time reaction even at low temperature.[4] Careful examination of the base-catalyzed reaction of the peroxy-*p*-quinol (**2a**) independently synthesized gave a clue to the present findings.



Results and Discussion

Base-Catalyzed Reaction of Peroxy-*p*-quinol 2a. The base-catalyzed reaction of **2a**[5] under nitrogen gave the

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