Bull. Chem. Soc. Jpn., 58, 1678—1682 (1985)

An Improved Preparation of the *p*-Tropoquinone Mono- and Diacetals by Thallium(III) Nitrate Oxidation of 2-Alkoxy-5-hydroxytropones

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(Received December 27, 1984)

The thallium(III) nitrate-oxidation of 2-alkoxy-5-hydroxytropones gave, in good yields, the mono- and diacetals of tropoquinones, which can be used for the introduction of oxygen functions to the seven-membered nucleus and preparation of the substituted tropoquinones. An improved synthesis of 4-methyl-*p*-tropoquinone or 4-methoxy-*p*-tropoquinone was accomplished.

We have previously synthesized a tropoquinone monoacetal, 7,7-ethylenedioxycyclohepta-2,5-diene-1,4-dione (**1**) by triethylamine-treatment and further manganese(IV) oxide oxidation of the endoperoxide of ethylenedioxytropone acetal (**2**) which can be prepared either by the dye-sensitized photooxidation of the corresponding tropone acetal (**3**) or by *p*-toluenesulfonic acid-catalyzed acetalization of the tropone endoperoxide (**4**).¹⁾ Since **1** and its derivatives may behave as typical unsaturated ketones and are useful for the synthesis of various seven-membered derivatives, it is important and desirable to develop more effective routes to obtain the acetal derivatives.

The oxidation of 5-hydroxytropolone (**5**) with silver acetate,²⁾ which is a one-electron oxidizing agent, was already shown to form the derivatives of either *p*-tropoquinone (**6**) or 2,10-dihydroxydicyclohepta[*b*,*d*]furan-3,9-dione (**7**) depending on the amounts of the oxidizing agent. Since the formation of **6** and **7** involved a common intermediate, the semiquinone radical, the yields of the derivatives of **7** should be improved by use of 5-hydroxy-2-methoxytropone (**8**) or its derivatives; unlike those from free 5-hydroxytropolones, the semiquinone radical derived from **8** is not convertible to **6**.³⁾ Taking these two points into account, it is predictable that the oxidation of **8** with an appropriate two-electron oxidizing agent in methanol may produce the acetal, 7,7-dimethoxy-2,5-cycloheptadiene-1,4-dione (**9**) but not **7**. Indeed, DDQ (2,3-dichloro-5,6-dicyano-*p*-benzoquinone) was effective for the purpose; as a preliminary study, we have employed it to obtain 4-methyl-*p*-tropoquinone (**10**).⁴⁾ Even more, thallium(III) nitrate (TTN)⁵⁾ seems to be a favorable choice, and **8** was accordingly oxidized in

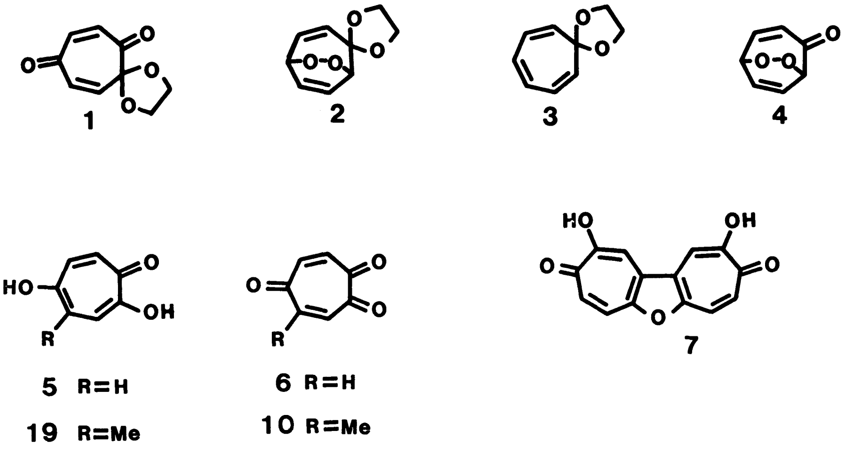
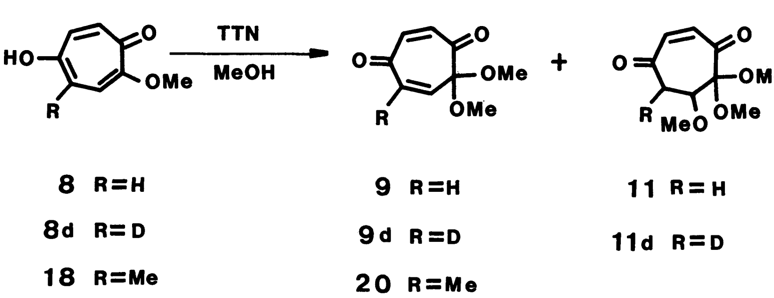


Chart 1.



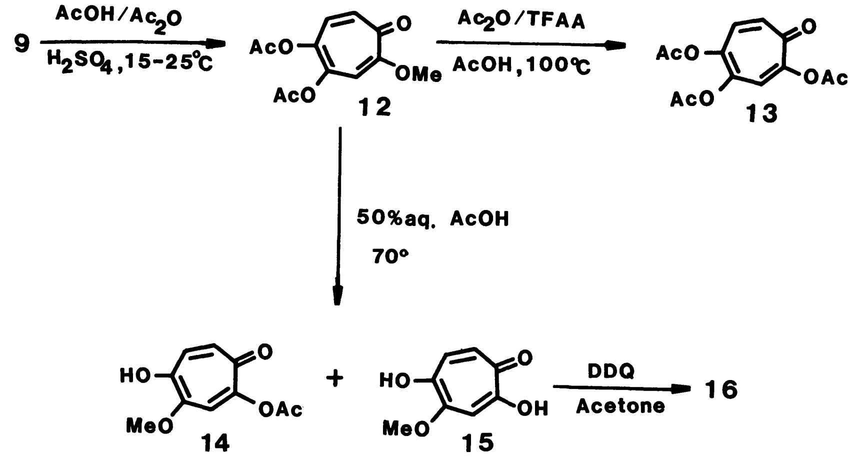
Scheme 1.

methanol at 15—25 °C for 4 h; the products obtained after brief work up were indeed **9**, a colorless oil, 90% yield, and its Michael type adduct, 5,5,6-trimethoxy-2-cycloheptene-1,4-dione (**11**), a colorless oil, 8% yield. On the other hand, prolonged treatment of **9** with TTN in methanol gave **11** in 77% yield. The position of the newly introduced methoxyl group was established by an aid of deuterio derivative of **8** (**8d**). Thus, heating of **8** in deuterium oxide yielded 5-hydroxy-2-methoxytropone-4-*d* (**8d**), whose ^{1}H NMR spectrum showed a disappearance of C-4 proton, δ=6.74.[6] The treatment of **8d** with TTN gave corresponding deuterio derivatives of **9** and **11** (**9d** and **11d**), 8% and 40% yields, respectively. The ^{1}H NMR spectrum of **11d** showed a diminishment of the signal at δ=2.87, together with change of splitting patterns of the proton signal (to d, J=4 Hz) at 3.95, ascribable to the proton on the carbon bearing the methoxyl group. Consequently, the position of the methoxyl group is C-6.

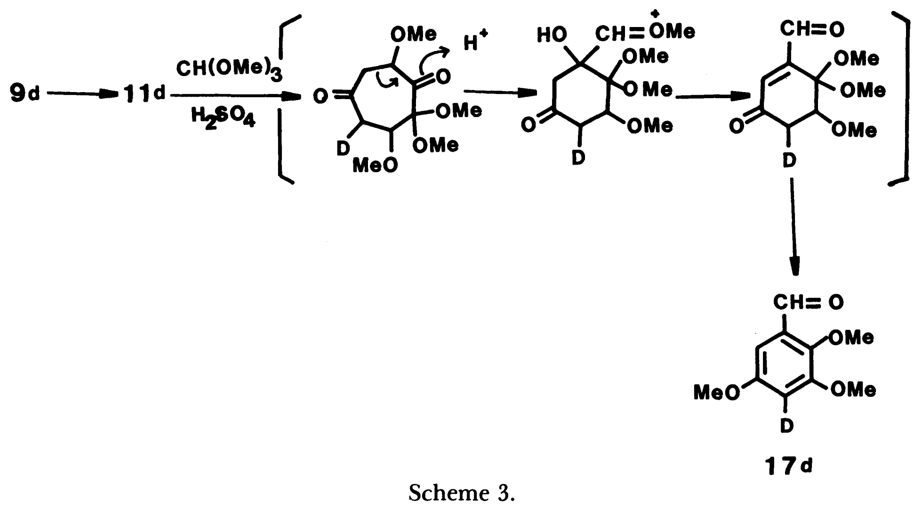
In parallel to this facile Michael reaction, the acetals smoothly underwent the Thiele-type addition reaction; *e.g.*, the brief treatment of **9** with a 1:1-mixture of acetic acid and acetic anhydride with a catalytic amount of sulfuric acid at 15—25 °C gave 4,5-diacetoxy-2-methoxytropone (**12**) in nearly quantitative yield.

The structure of **12** was obtained on the basis of the NMR spectral analysis as well as chemical derivations; thus, the further treatment of **12** with trifluoroacetic anhydride (TFAA) and acetic anhydride in acetic acid gave colorless crystalline triacetoxytropone (**13**). A mild hydrolysis of **12** with aqueous acetic acid afforded 2-acetoxy-5-hydroxy-4-methoxytropone (**14**) and 5-hydroxy-4-methoxytropolone (**15**), the latter of which was oxidized with DDQ to a derivative which must be 4-methoxy-*p*-tropoquinone (**16**): *i.e.*, the ^{1}H NMR spectrum of **16** revealed a 1H-singlet at δ=6.22, and a lack of the long-range coupling with other aromatic protons at 6.80 and 6.94, appearing as an AB pair (J=13 Hz), ruled out the possibility of the methoxyl group at C-3, whose singlet appeared at 3.90. Previously, the Thiele reaction of **6** itself was carried out by Hirama and Itô to form 2,4,7-triacetoxytropone in 7% yield by acetic anhydride and sulfuric acid;[7] the improvement of the yield of the present results was thus satisfactory and the site of the attack indicated the reaction should have been started by the protonation on the acetal oxygen.

Other than this, the attempted hydrolysis of **9** under modified conditions tends to cause a ring contraction to the benzenoid derivative; thus, the reaction of **9** or



Scheme 2.



Scheme 3.

11 with trimethoxymethane and sulfuric acid gave 2,3,5-trimethoxybenzaldehyde (**17**),[8] as the only identifiable product in 51 and 76% yields, respectively. Its formation mechanism, shown in Scheme 3, was verified by an aid of **9d**; the deuterium in **17d** was determined to be at C-4.

In general, a conversion of **5** to **6** has been achieved by the DDQ oxidation, however, sometimes there were experimental difficulties, *e.g.*, in order to prepare **10**, we have prepared 5-hydroxy-2-methoxy-4-methyltropone (**18**) by sequential reactions from **8**,[4] but every attempt to hydrolyze **18** to 5-hydroxy-4-methyltropolone (**19**) was unsuccessful. Alternatively, **18** was oxidized with DDQ in methanol to 7,7-dimethoxy-5-methyl-2,5-cycloheptadiene-1,4-dione (**20**), whose mild hydrolysis is known to afford the desired **10**.[4] For the formation of **20** from **18**, TTN was much superior than DDQ; the yield was 98%.

Furthermore, the TTN-oxidation of 5-hydroxy-2-(2-hydroxyethoxy)tropone (**21**) in methanol gave a crystalline diacetal, 4,5-dimethoxy-4,5-(ethylenedioxy)-2,6-cycloheptadien-1-one (**22**), 28%, and its monohemiacetal, the crystalline 4-hydroxy-5-methoxy derivative (**23**), 57%. The stereochemistry of **22** was shown to be trans on the basis of NMR observations of its dihydro derivative (**24**); *i.e.*, in the ^{1}H NMR spectrum, two methyl signals appeared separately, and the ^{13}C NMR spectrum exhibited all non-overlapped eleven signals. The **22** and **23** were also acetoxylated with acetic anhydride and sulfuric acid in acetic acid at room temperature for 3 h to 6-acetoxy-2,3-(ethylenedioxy)tropone (**25**)[9] through a rearrangement.

In conclusion, the present method provided a convenient entry to *p*-tropoquinone acetals, which are versatile intermediates for various functionalized troponoids. However, this method was not applicable to the free tropolone derivatives like 5-methoxytropolone; by the addition of TTN, the substrates precipitated out by salt formation, and prevented the oxidation to be taken place.

Some new aspects of the tropoquinone chemistry developed therefrom will be reported in future.

Experimental

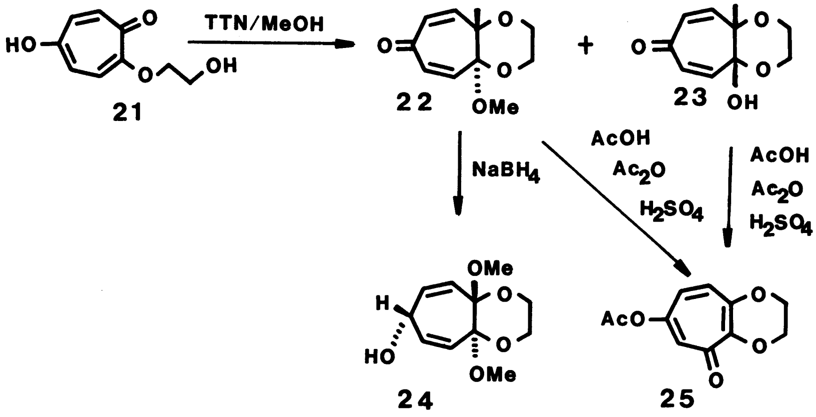
Elemental analyses were performed by Miss S. Hirashima at this Institute. The mps were measured by a Yanagimoto Micro-mp Apparatus and were uncorrected. The IR spectra were taken as KBr disks with a Jasco Model A 102 Spectrometer. The NMR spectra were measured in CDCl$_3$ solution, unless otherwise specified, by a JEOL FX 100 Model Spectrometer, and the chemical shifts were expressed in the δ unit from the internal Me$_4$Si. The mass spectra were measured on a JEOL 01SG-2 Model Spectrometer.

TTN-Oxidation of 5-Hydroxy-2-methoxytropone (8). a) An anhydrous MeOH solution (12 cm^3) of **8** (400 mg) was treated with TTN (1.17 g) at −20 °C, and the mixture was kept with stirring at 15—25 °C for 0.5 h. Silica-gel column chromatography of the mixture afforded a colorless oil, **9**, 430 mg (90%) [Found: M$^+$, 182.0574. Calcd for $C_9H_{10}O_4$: M$^+$, 182.0577. ^{1}H NMR δ=3.36 (6H, s), 6.25 (1H, dt, *J*=12, 1 Hz), 6.43 (1H, d, *J*=12 Hz), and 6.49 (2H, d, *J*=1 Hz). ^{13}C NMR δ=50.7 (2C), 103.0, 133.5, 133.8, 136.7, 138.9, 190.8, and 192.7], and a colorless oil, **11**, 45 mg (8%) [Found: C, 55.77; H, 6.55%. Calcd for $C_{10}H_{14}O_5$: C, 56.07; H, 6.59%. ^{1}H NMR δ=2.87 (1H, dd, *J*=17, 3.8 Hz), 3.18 (1H, dd, *J*=17, 3.8 Hz), 3.18 (3H, s), 3.37 (3H, s), 3.40 (3H, s), 3.94 (1H, t, *J*=3.8 Hz), 6.34 (1H, d, *J*=13 Hz), and 6.54 (1H, d, *J*=13 Hz). ^{13}C NMR δ=43.4, 49.6, 50.9, 58.6, 75.5, 103.6, 133.4, 138.1, 193.4, and 197.3. $\lambda_{\max}^{\mathrm{CHCl_3}}$: 243 nm (ε=6900), 348 (1400). *m/z*: 182 (M$^+$−32), 75 (base peak)].

b) Prolonged treatment of the mixture of **8** (30 mg) and TTN (88 mg) in MeOH (0.5 cm^3) at 15—25 °C for 10 h and then at 50 °C for 2 h resulted in the formation of **11**, 33 mg (77%).

Preparation of Deuterio Derivative of 8 (8d). A mixture of **8** (1 g) and D_2O (10 cm^3) containing AcOH (50 mg) was heated at 90 °C for 23 h in a sealed tube. After cooling the mixture, yellow crystals (850 mg) [*m/z*, 152, 153, 154 (11:86:3). ^{1}H NMR (CD$_3$OD) δ=3.83 (3H, s), 6.5—6.8 (0.1H), 7.08 (1H, s), and 7.10 (2H, s)] obtained by filtration was identified to be **8d**.

TTN-Oxidation of 8d to 9d and 11d. An anhydrous MeOH solution (1 cm^3) of **8d** (50 mg) was treated with TTN (150 mg) under the same conditions to those of deuterium-free **8**. Silica-gel chromatography of the mixture afforded **9d**, 5 mg (8.5%) [*m/z*, 182, 183, 184 (18:76:6). ^{1}H NMR δ=3.30 (6H, s), 6.42 (1.2H, m), and 6.50 (1.8H, s)], and **11d**, 28 mg



Scheme 4.

(40%) [m/z, 183 (M^+-32), 182 (M^+-33), 75 (base peak). ^{1}H NMR δ=2.8—3.1 (1.2H, m), 3.18 (3H, s), 3.37 (3H, s), 3.41 (3H, s), 3.95 (1H, d, J=4 Hz), 6.34 (1H, d, J=13 Hz), and 6.51 (1H, dm, J=13 Hz)].

*Reaction of **9** with Ac_2O and H_2SO_4.* A mixture of **9** (50 mg), Ac_2O (0.3 cm^3), AcOH (0.3 cm^3), and H_2SO_4 (20 mg) was stirred at 15—25 °C for 0.5 h. Silica-gel column chromatography of the mixture afforded colorless needles, mp 116—117 °C, 46 mg (98%), **12** [Found: C, 57.14; H, 4.80%. Calcd for $C_{12}H_{12}O_6$: C, 57.03; H, 4.67%. ^{1}H NMR δ=2.28 (3H, s), 2.32 (3H, s), 3.80 (3H, s), 6.65 (1H, d, J=10.5 Hz), 6.70 (1H, s), and 6.91 (1H, d, J=10.5 Hz). ^{13}C NMR δ=20.4, 20.6, 56.5, 116.7, 121.0, 122.1, 148.2, 159.1, 168.2, 168.5, and 176.2. $\lambda_{\max}^{CHCl_3}$: 247 nm (ε=38000), 257 (26000), 308 (5300)], and the recovered **9**, 16 mg.

*Conversion of **9** to 2,4,5-Triacetoxytropone (**13**).* A mixture of **9** (120 mg), Ac_2O (5 cm^3), TFAA (0.3 cm^3), and AcOH (60 mg) was heated at 100 °C for 4.5 h. The mixture was heated *in vacuo* to remove the solvents, and the residue chromatographed on a silica-gel column to give colorless needles, mp 121.5—123 °C, 23 mg (17%),[10] **13** [Found: C, 55.69; H, 4.31%. Calcd for $C_{13}H_{12}O_7$: C, 55.72; H, 4.32%. ^{1}H NMR δ=2.26 (6H, s), 2.32 (3H, s), 6.89 (1H, d, J=11.5 Hz), 7.06 (1H, s), and 7.11 (1H, d, J=11.5 Hz). ^{13}C NMR δ=20.4, 20.6, 20.8, 121.9, 123.5, 129.9, 146.5, 153.6, 153.8, 166.1, 167.2, 167.5, and 167.8].

*Controlled Hydrolysis of **12** to **14** and **15**.* A 50%-aqueous AcOH solution (3 cm^3) of **12** (1.2 g) was heated at 70 °C for 2 d. The mixture was heated *in vacuo* to remove the solvent, the residual mass was chromatographed on a silica-gel column to give colorless needles, mp 127—128 °C, 420 mg (42%), **14** [Found: C, 57.04; H, 4.83%. Calcd for $C_{10}H_{10}O_5$: C, 57.14; H, 4.80%. ^{1}H NMR δ=2.28 (3H, s), 3.86 (3H, s), 6.83 (1H, d, J=11 Hz), 6.93 (1H, s), and 6.96 (1H, d, J=11 Hz). ^{13}C NMR δ=20.3, 56.6, 109.1, 110.8, 126.6, 142.7, 161.1, 162.4, 168.9, and 175.6. $\lambda_{\max}^{CHCl_3}$: 250 nm (ε=31500), 267 (15000), 325 (6400), 340 (4800), 355 (3600)], and pale yellow crystals, mp 209 °C, 250 mg (31%), **15** [Found: M$^+$, 168.0423. Calcd for $C_8H_8O_4$: 168.0423. ^{1}H NMR $\delta(CD_3OD)$=4.14 (3H, s), 7.52 (1H, d, J=12 Hz), 7.64 (1H, d, J=12 Hz), and 7.67 (1H, s). ^{13}C NMR δ=58.2, 115.0, 125.5, 126.6, 158.1, 158.9, 161.6, and 165.3. $\lambda_{\max}^{MeOH}$: 248 nm (ε=29600), 344 (11400). ν: 3100—2500, 1600, 1520, 1450—1400 cm^{-1}].

*Synthesis of 4-Methoxy-*p*-tropoquinone (**16**) from **15**.* An MeOH solution (2 cm^3) of **15** (50 mg) was mixed with DDQ (68 mg) and kept at 15—25 °C for 30 min. Silica-gel column chromatography of the mixture gave a yellow oil, 30 mg (61%), **16** [Found: M$^+$, 166.0267. Calcd for $C_8H_6O_4$ 166.0267. ^{13}C NMR δ=57.3, 108.8, 134.3, 137.6, 160.8, 181.5, 183.5, and 184.7].

*The Reaction of **9** with Trimethoxymethane and H_2SO_4.* A mixture of **9** (55 mg), $CH(OMe)_3$ (0.1 cm^3), MeOH (0.5 cm^3), and H_2SO_4 (30 mg) was kept at 15—25 °C for 1 h. Colorless crystals obtained, **17**, mp 62 °C, 30 mg (52%), was identified to be 2,3,5-trimethoxybenzaldehyde (lit,[8] mp 67 °C) [^{1}H NMR δ=3.80 (3H, s), 3.83 (3H, s), 3.85 (3H, s), 6.73 (1H, d, J=3 Hz), 6.83 (1H, d, J=3 Hz), and 10.38 (1H, s)].

*The Reaction of **9d** with Trimethoxymethane and H_2SO_4.* Similar to above, **9d** (75 mg) was treated in MeOH (1.5 cm^3) with $CH(OMe)_3$ (0.15 cm^3) and H_2SO_4 (50 mg) to give **17d**, 58 mg (72%) [^{1}H NMR δ=3.78 (3H, s), 3.85 (3H, s), 3.90 (3H, s), 6.72 (0.65H, d, J=3 Hz), 6.81 (0.65H, d, J=3 Hz), 6.81 (0.35H, s), and 10.32 (1H, s). m/z: 196, 197, 198 (68:29:3)].

*The Reaction of **11** with Trimethoxymethane and H_2SO_4.* Similarly, a mixture of **11** (40 mg), $CH(OMe)_3$ (0.1 cm^3), MeOH (2 cm^3), and H_2SO_4 (30 mg) was kept at 50 °C for 2 h. The product isolated was **17**, 28 mg (76%), identical in every respect to the sample prepared from **9**.

*TTN-Oxidatin of **18** in MeOH to 7,7-Dimethoxy-5-methyl-2,5-cycloheptadiene-1,4-dione (**20**).* An anhydrous MeOH solution (1.5 cm^3) of **18** (45 mg), prepared as previously,[4] was treated with TTN (120 mg) at −20 °C, and gradually raised the temperature to 20 °C within 1 h. The silica-gel chromatography of the mixture afforded **20**, 50 mg (93%).[4]

*TTN-Oxidation of 5-Hydroxy-2-(2-hydroxyethoxy)tropone (**21**) in MeOH.* To an anhydrous MeOH suspension (1.5 cm^3) of **21** (30 mg) which was prepared as previously,[1] TTN (73 mg) was added at −20 °C. After standing at 20 °C for 1 h, the mixture was chromatographed on a silica-gel column to give colorless crystals, mp 108—109 °C, 10.4 mg (28%), **22** [Found: C, 58.60; H, 6.22%. Calcd for $C_{11}H_{14}O_5$: C, 58.40; H, 6.24%. ^{1}H NMR δ=3.27 (6H, s), 3.8 (4H, m), 6.09 (2H, d, J=12.5 Hz), and 6.28 (2H, d, J=12.5 Hz). ^{13}C NMR δ=50.1 (2C), 58.8 (2C), 96.8 (2C), 131.3 (2C), 141.9 (2C), and 189.8], and colorless crystals, mp 123—124 °C, 20 mg (57%), **23** [Found: C, 56.46; H, 5.67%. Calcd for $C_{10}H_{12}O_5$: C, 56.60; H, 5.70%. ^{1}H NMR δ=3.29 (3H, s), 3.5—3.7 (2H, m), 3.9—4.5 (2H, m), 6.02 (1H, d, J=13 Hz), 6.14 (1H, d, J=13 Hz), 6.32 (1H, d, J=13 Hz), and 6.37 (1H, d, J=13 Hz). ^{13}C NMR δ=50.1, 58.6, 58.9, 93.5, 97.0, 129.9, 131.6, 142.2, 144.0, and 190.3].

*$NaBH_4$-Reduction of **22** to Dihydro Derivative (**24**).* An MeOH solution (2 cm^3) of **22** (30 mg) was mixed with $NaBH_4$ (12 mg) at 0 °C, and kept 1d at 15—25 °C. Silica-gel column chromatography of the mixture afforded colorless needles, mp 105—107 °C, 17 mg (56%), **24**, [Found: M$^+$, 228.0991. Calcd for $C_{11}H_{16}O_5$: 228.0996. ^{1}H NMR δ=3.26 (3H, s), 3.30 (3H, s), 3.4—4.1 (4H, m), 4.90 (1H, qd, J=2.5, 2 Hz), 5.49 (1H, dd, J=11.5, 2.5 Hz), 5.50 (1H, dd, J=12.5, 2 Hz), 5.86 (1H, ddd, J=12.5, 2.5, 1.7 Hz), and 5.98 (1H, ddd, J=11.5, 2.5, 1.7 Hz). ^{13}C NMR δ=49.2, 49.3, 58.4, 58.6, 68.7, 95.3, 97.8, 127.3, 128.6, 134.1, and 136.8. ν: 3520 cm^{-1}].

*Modified Thiele Reaction of **22** to **25**.* A mixture of **22** (16 mg), Ac_2O (0.5 cm^3), AcOH (0.5 cm^3), and H_2SO_4 (30 mg) was kept at 15—25 °C for 3 h. After dilution with water, the mixture was extracted with ether. Silica-gel column chromatography of the extract gave a colorless oil, 10 mg (64%), **25** [Found: C, 59.31: H, 4.57%. Calcd for $C_{11}H_{10}O_5$: C, 59.46; H, 4.54%. ^{1}H NMR δ=2.26 (3H, s), 4.2—4.5 (4H, m), 6.53 (1H, dd, J=12.5, 2.8 Hz), 6.90 (1H, dd, J=12.5, 0.5 Hz), and 6.93 (1H, dd, J=2.8, 0.5 Hz), whose *ABC* system was deduced by simulation. ^{13}C NMR δ=21.0, 63.8, 64.0, 124.4, 129.3, 129.9, 147.5, 148.7, 154.6, 168.6, and 176.6].

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9) The structure of **25** was deduced on the NMR and UV spectral evidence, *i.e.*, i) δ=176.6 in the ^{13}C NMR is attributable to the carbonyl carbon of a 2-alkoxytropone, ii) J_{vic}= 12.5 Hz of δ=6.53 (H-4) and 6.90 (H-5) indicates the retention of the tropone system [λ_{max}^{MeOH} = 225 nm (log ε=4.11), 254 (4.42), 261 (4.35), 298 (3.53), 307 (3.66), 319 (3.51), 357 (3.56), 370 (3.51)], which constituted an *ABC* system with one more proton at δ=6.93 (H-7), and iii) $\Delta\delta$=0.40 between H-4 and H-5 must be explained in terms of the upfield shift due to the acetoxyl group on C-6. These observations are compatible with only the structure depicted.

10) Improved procedure of this acetolysis will be a subject of an independent paper.