The Synthesis of Several Alkyl-p-tropoquinones

Mori, Akira
Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University

Isayama, Yasutoshi
Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University

Kusaba, Tomoyuki
Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University

Takeshita, Hitoshi
Department of Molecular Science and Technology, Interdisciplinary Graduate School of Engineering Sciences, Kyushu University

https://doi.org/10.15017/17606

出版情報：九州大学大学院総合理工学報告. 6 (2), pp.185-191, 1985-01-01. 九州大学大学院総合理工学研究科
バージョン：
権利関係：

The Synthesis of Several Alkyl-*p*-tropoquinones

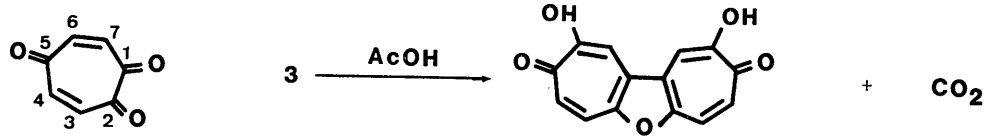
Akira MORI, Yasutoshi ISAYAMA, Tomoyuki KUSABA
and Hitoshi TAKESHITA*

(Received September 29, 1984)

Synopsis. The Claisen rearrangment products and the Mannich reaction products of some 5-hydroxytropolone derivatives were conveniently converted to the *p*-tropoquinones in good yield. A facile preparation of alkenyl-*p*-tropoquinones may be valuable for further conversion to the functional derivatives.

Up to date, only the alkyl-*p*-tropoquinones synthesized are 3, 7-dimethyl (**1**)[1] and 4-isopropyl (**2**)[2] derivatives. In general, troponoids are not applicable to metal-catalyzed electrophilic substitutions, such as Friedel-Crafts reaction, and moreover, due to the *o*, *p*-directivity in respects of the *α*-hydroxyketone function, analogous to phenols, the electrophilic substitution gives the 3, 5, 7-substituted derivatives. Consequently, an introduction of substituents on the C-4 position is difficult. In connection to our recent study of the reductive dimerization of *p*-tropoquinone (**3**) in acetic acid to the so-called phenol oxidation product, 2, 10-dihydroxycyclohepta[*b*,*d*]-furan-3, 9-dione (**4**), which was accompanied by an evolution of carbon dioxide,[3] we needed a series of **3** derivatives, which might be higher in oxidation potentials than the benzoquinone derivatives in view of the existence of the ortho and para quinone moieties within the molecules. We now synthesized several **3** derivatives having electron-releasing substituents, such as methyl-, propyl-, and allyl groups on the C-4 and/or C-6 positions, together with some 3, 6-dialkyl derivatives. Several electron-attractive halogeno derivatives of **3** have been already prepared[4].

For preparation of 4-monoalkyl derivatives by Mannich reaction, it is necessary to modify the troponoid functions as the reaction usually gives polysubstituted derivatives, but is an attractive way to introduce C_1 units in view of either easy conversion to the methyl group by hydrogenolysing the amino



1: Me at 3 and 7
2: Me_2CH at 4
3: unsubstituted

4

[Scheme 1]

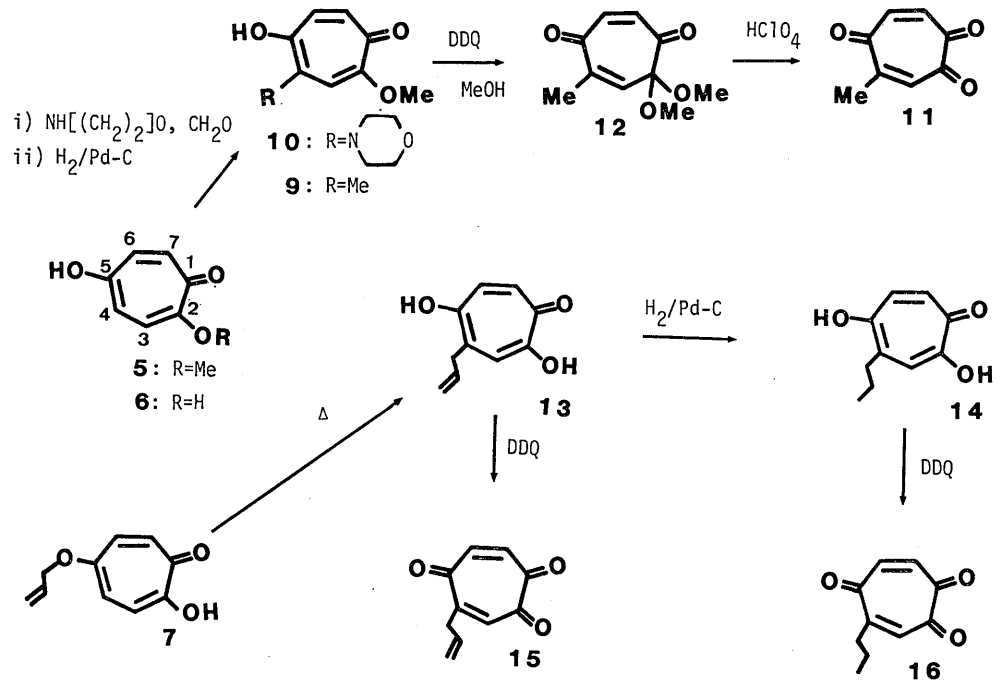
* Department of Molecular Science.

group, or versatility toward various functional groups. On the other hand, Claisen rearrangement, another entry, has some prospect in the C-4 bond formation from our previous study on the bifunctional troponoids.

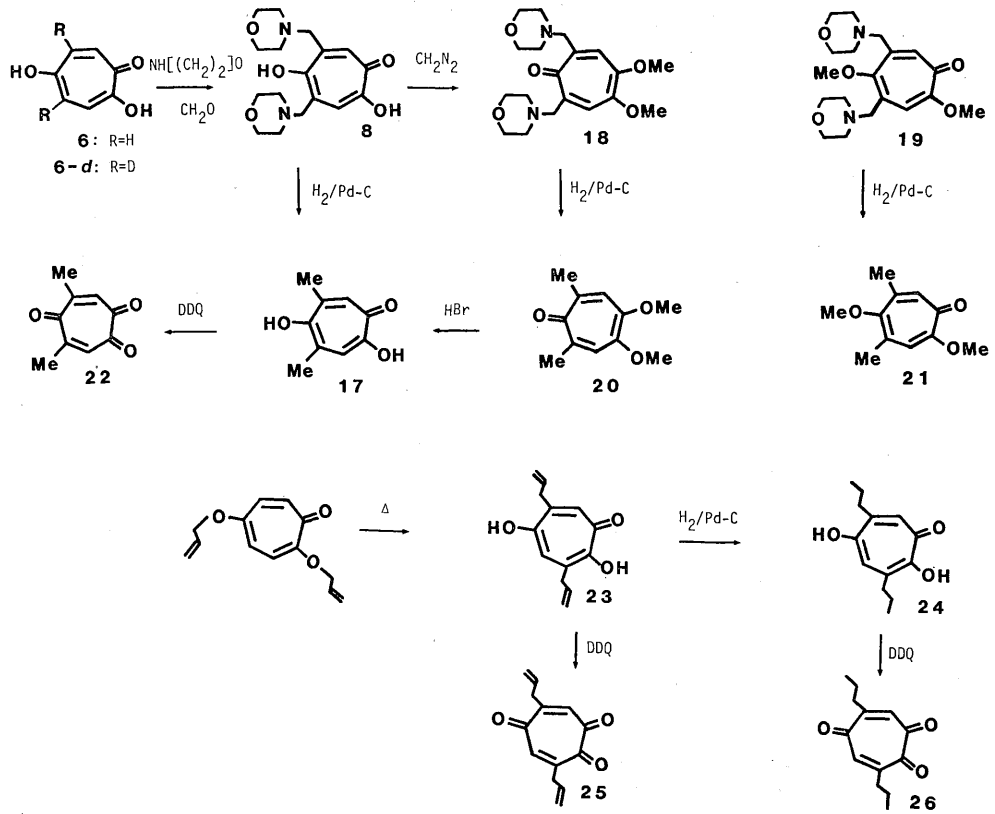
In either case, the C-2 hydroxyl group of the tropolone ring needed to differentiate or protect over C-5 oxygen function. In this regard, we have already developed a method to prepare 5-hydroxy-2-methoxytropone (**5**) from 5-hydroxytropolone (**6**) by a three-step sequence; *i.e.*, acetylation of **6** gave the diacetate, and, upon a mild hydrolysis, it afforded 5-acetoxytropolone, whose methylation by diazomethane and subsequent hydrolysis yielded desired **5**.

The Claisen rearrangement was also applicable for the purpose as metioned, 4-allyltropolones could be synthesized i) from 2,5-di(allyloxy)tropones through a selective mono-deallylation of the C-2 functions,[5] or ii) the preferential C-5 allylation of **6** and consecutive Claisen rearrangement.[6] Indeed, 5-(allyloxy)-tropolone (**7**) was prepared in straightforward by the latter method.

On the other hand, preparations of dialkyl derivatives were even much easier: Claisen rearrangement of 2,5-di-(allyloxy) tropones was shown to form 3,6-diallyl derivatives, and although the Mannich reaction of **6** itself has been previously unknown, the reaction of **6** with morpholine (MP) and formaldehyde (FA) at room temperature indeed gave a single product (**8**). The structure of **8** was deduced by comparisons with the product of isotope-labelled compound: The reaction with the deuterio-5-hydroxytropolone (**6**-*d*) obtained by treat-



[Scheme 2]



〔Scheme 3〕

ment with deuterium oxide, among which the 4, 6-dideuterio derivative (**6**-d_2) being predominant, gave the corresponding dimorpholinomethyl derivative (**8**-d_n). According to the NMR spectrometry, this **8**-d_n has retained only fragmental quantity of deuterium on the C-3 and C-7 positions. Therefore, **8** is 4, 6-di-(morpholinomethyl)tropolone.

By these methods, 4-methyl (**11**), 4, 6-dimethyl (**22**), 4-allyl (**15**), 3, 6-diallyl (**25**), 4-propyl (**16**), and 3, 6-dipropyl (**26**) derivatives have been prepared. Particularly noteworthy was a ready introduction of propenyl group on the tropoquinone nucleus which might be important for further conversions of *p*-tropoquinones.

Currently, we are undertaking the studies on this line.

Experimental

5-Hydroxy-2-methoxy-4-methyltropone (**9**). 5-Hydroxy-2-methoxytropone (**5**, 100 mg) derived from 5-hydroxytropolone (**6**) by three steps, was mixed with morpholine (MP, 126 mg) and 37 %-aqueous solution of formaldehyde (FA, 0.1 cm³) at 0–5°C, and kept at 15–25°C for 15 h to form 5-hydroxy-2-methoxy-4-(morpholinomethyl)tropone (**10**) [Found: C, 62.18; H, 6.87; N, 5.80 %. Calcd for $C_{13}H_{17}O_4N$: C, 62.14; H, 6.82; N, 5.57 %. ^{1}H NMR δ (CD_3OD) = 2.6–2.7(4H, m), 3.6–3.9(6H, m), 3.88(3H, s), 7.08(1H, s), and 7.18(2H,s). ^{13}C NMR(CD_3OD) δ = 53.5, 57.0, 64.5, 76.5,

122.4, 135.1, 137.3, 158.7, 163.4, and 178.0], mp 250℃ (decomp), 164 mg (100 %). Subsequent hydrogenolysis of **10**(100 mg) by Pd on carbon afforded 5-hydroxy-2-methoxy-4-methyltropone (**9**), mp 199–202℃ [Found: C, 64.77; H, 6.02 %. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07 %. ^{1}H NMR δ= 2.32(3H, s), 3.91(3H, s), 7.18(2H, s), and 7.27(1H, s). ^{13}C NMR(CD_3OD) δ = 21.7, 57.3, 125.9, 132.7, 133.5, 134.8, 157.0, 165.4, and 171.4), colorless needles, mp 199–202℃, 66 mg (86 %).

Attempted Hydrolysis of ***9***. An AcOH solution (2 cm^3) of **9** (5 mg) was heated under acidic conditions with mineral acid, which is known to be effective for hydrolysis of methoxytropones to tropolones. However, in every time it resulted in the recovery of **9**, or extensive decomposition of the material.

*4-Methyl-*p*-tropoquinone*(***11***). An anhydrous MeOH solution (1 cm^3) of **9** (30 mg) was treated with DDQ (2, 3-dichloro-5, 6-dicyano-*p*-benzoquinone, 40 mg) at 15–25℃ for 0.5 h to give the dimethyl acetal (**12**)[7] [Found: M. W. 196.0733. Calcd for $C_{10}H_{12}O_3$: M.W., 196.0733. ^{1}H NMR (CD_3OD)[8] δ =1.93 (3H, d, J=1.7 Hz), 3.22(6H, s), 6.13 (lH, q, J=1.7 Hz), 6.37 (1H, d, J=12.5 Hz), and 6.54(1H, J= 12.5 Hz). ^{13}C NMR (CD_3OD) δ =19.6, *(2C signals underneath the solvent signals), 104.3, 133.1, 133.4, 139.4, 144.1, 185.6, 194.4, and 195.6], a yellow oil, whose subsequent hydrolysis with 1 N perchloric acid in aqueous acetone, furnished 4-methyl-*p*-tropoquinone (**11**) [Found: C, 63.93; H, 4.17 %. Calcd for $C_8H_6O_3$: C, 64.00; H, 4.03 %. δ =2.20 (3H, d, J=1.2 Hz), 6.75 (1H, d, J=12.5 Hz), 6.85 (1H, q, J=1.2 Hz), and 6.92 (1H, d, J=12.5 Hz). ^{13}C NMR δ =21.1, 133.0, 133.2, 140.0, 148.5, 185.6, 186.0, and 187.9], pale yellow crystals, mp 55–56℃, 17.4 mg (74 %).

4-Allyl-5-hydroxytropolone (***13***). A xylene solution (3 cm^3) of **7** (317 mg, mp 134–136 ℃; *lit.* 137–138℃)[6] was refluxed for 6 h. The silica-gel column chromatography of the mixture afforded 4-allyl-5-hydroxytropolone (**13**) [Found: C, 67.23; H, 5.64 %. Calcd for $C_{10}H_{10}O_3$: C, 67.40; H, 5.66 %. ^{1}H NMR δ =3.44(2H, d, J=6.5 Hz), 5.0–5.2(2H, m), 5.96 (1H, ddt, J=17, 10, 6.5 Hz), 7.04(1H, d, J=12 Hz), 7.21 (1H, d, J=12 Hz), and 7.38(1H, s). ^{13}C NMR δ =39.6, 116.9, 123.9, 124.4, 130.3, 135.9, 140.7, 158.5, 166.4, and 168.8], colorless needles, mp 195–197℃, 310 mg (98 %).

Catalytic Hydrogenation of ***13***. In an ordinary manner, **13**(30 mg) in MeOH was reduced, by Pd on carbon, to 5-hydroxy-4-propyltropolone (**14**) [Found: C, 66.39 H, 6.72 % Calcd for $C_{10}H_{12}O_3$: C, 66.65; H, 6.71 %. ^{1}H NMR (CD_3OD) δ =0.98 (3H, t, J=7.2 Hz), 1.64(2H, sext, J=7.2 Hz), 2.68(2H, t, J=7.2 Hz), 7.02 (1H, d, J=11.8 Hz), 7.19 (1H, d, J=11.8 Hz), and 7.39(1H, s). ^{13}C NMR(CD_3OD) δ =14.3, 24.0, 38.7, 124.0, 124.4, 131.4, 144.1, 159.2, 166.5, and 169.8], pale yellow needles, mp 193–196℃, 26.5 mg (87 %).

DDQ-dehydrogenation of ***13***. An acetone solution (3 cm^3) of **13** (25 mg) was treated with DDQ (32 mg) at 15–25℃ for 4 h to give 4-allyl-*p*-tropoquinone (**15**) [Found: C, 67.98; H, 4.47 %. Calcd for $C_{10}H_8O_3$: C, 68.18; H, 4.58 %. ^{1}H NMR δ = 3.32(2H, dq, J=6.5, 1.2 Hz), 5.18(1H, ddt, J=16, 1.5, 1.2 Hz), 5.23(1H, ddt, J= 10.5, 1.5, 1.2 Hz), 5.82(1H, ddt, J=16, 10.5, 6.5 Hz), 6.74 (1H, d, J=13 Hz), 6.80 (1H, t, J=1.2 Hz), and 6.95(1H, d, J= 13 Hz). ^{13}C NMR δ =37.5, 119.8, 132.6, 133.0 (2C), 140.2, 150.4, 185.6, 186.3,

and 187.6], 11 mg (45 %), pale yellow crystals, mp 27–28℃.

DDQ-dehydrogenation of ***14***. Similarly, an acetone solution (3 cm³) of **14** (30 mg) was treated with DDQ (37 mg) to give, after silica-gel column chromatography, a pale yellow oil, 4-propyl-*p*-tropoquinone (**16**) [Found: C, 76.13; 5.71 %. Calcd for $C_{10}H_{10}O_3$: C, 67.40; H,5.66 %. ^{1}H NMR δ =0.97(3H, t, J=7 Hz), 1.54(2H, sext, J=7 Hz), 2.55(2H, td, J=7, 1.2 Hz), 6.60(1H, d, J=13 Hz), 6.78 (1H, t, J=1.2 Hz), and 6.90(1H, d, J=13 Hz). ^{13}C NMR δ =13.8, 22.0, 36.0, 132.6, 132.9, 140.4, 152.4, 185.6, 186.2, and 188.0], a faintly reddish oil, 25.2 mg (85 %).

5-Hydroxy-4,6-di(morpholinomethyl)tropolone (***8***). A mixture of **6** (500 mg), MP (1.3 cm³) and aqueous FA (1.4 cm³) was kept at 15–25℃ for 10 to 15 h to precipitate a crystalline solid, di(morpholinomethyl) derivative (**8**) [Found: C, 60.42; H, 7.13; N, 8.29 %. Calcd For $C_{17}H_{24}O_5N_2$: C, 60.70; H, 7.19; N,8.33 %. ^{1}H NMR δ =2.5–2.7(8H, m), 3.6–3.9(12 H, m), 7.47(2H, s), and 9.10(2H, s). ^{13}C NMR(CD_3OD) δ =53.0 (4C), 63.0 (2C), 66.6 (4C), 125.7(2C), 132.3(2C), 159.7, and 166.6(2C)], pale yellow needles, mp>300℃, 1.17 g (96 %). With less than stoichiometric amounts of reagents, still the product was solely **8** other than the recovered **6**.

Deuteration of **6** *to 4,6-Dideuterio-5-hydroxytropolone* (***6***-d). A D_2O solution (10 cm³) of **6** (975 mg) was heated in a sealed tube at 175–180℃ for 20 h. After cooling, the solidified compound was collected by filtration to mainly give **6**-d_2, 970 mg, as pale yellow solid, mp 242℃ (decomp) [Found: M.W., m/z, 138, 139, 140, 141, and 142 (0 : 4.2 : 50 : 34 : 10)].

Morpholinomethylation of **6**-d. A mixture of **6**-d_2 (37 mg), MP (111 mg) and aqueous FA (33 mg) was kept at 15–25℃ for 15 h. The resultant precipitates were collected by filtration, and recrystallized from $CHCl_3$ and hexane to yield pale yellow powder, mp>300℃, 34.5 mg (97 %), which was identical with **8** in respect of the ^{1}H NMR in $CDCl_3$ [2.5–2.7(8H, m), 3.6–3.9(12H, m), 7.48(2H×0.7, s) and 9.10(2H, br. s)].

Catalytic Hydrogenolysis of ***8***. Similarly, **8** (300 mg) was reduced in AcOH with Pd on carbon to give 5-hydroxy-4,6-dimethyltropolone (**17**), mp 192–193℃ [Found: C, 65.18; H, 6.03 %. Calcd for $C_9H_{10}O_3$: C, 65.05; H, 6.07 %. ^{1}H NMR (CD_3OD) δ =2.36 (6H, s), 7.36 (2H, s). ^{13}C NMR (CD_3OD) δ =23.8, 129.1, 139.2, 163.0, and 163.3] in rather poor yield, 30 %.

Methylation of ***8***. A mixed solution of MeOH and acetone (7 cm³) of **8** (250 mg) was treated with diazomethane to give 4,5-dimethoxy-2,7-di(morpholinomethyl)-tropone (**18**) [Found: C, 62.67; H,7.77; N, 7.75%. Calcd for $C_{19}H_{28}O_5N_2$: C, 62.62; H, 7.74; N, 7.69 %. ^{1}H NMR δ =2.5–2.6 (8H, m), 3.6–3.8(12H, m), 3.96(6H, s), and 7.94(2H, s). ^{13}C NMR δ =53.2(4C), 57.8(2C), 59.7(2C), 67.0(4C), 126.6(2C), 142.1(2C), 150.0 (2C), and 181.4], pale yellow crystals, mp 108.5–109℃, 136 mg (50 %), and 2,5-dimethoxy-4,6-di(morpholinomethyl)tropone (**19**) [Found: C, 62.49; H, 7.73; N, 7.63 %. ^{1}H NMR δ = 2.4–2.6 (8H, m), 3.5–3.8(12H, m), 3.67(3 H, s), 3.90(3H, s), 7.33(1H, s), and 7.46 (1H, s). ^{13}C NMR δ =53.2(4C), 55.7, 58.4, 60.5, 61.6, 66.0(2C), 66.8(2C), 113.3, 133.0, 135.9, 143.6, 156.2, 160.8, and 178.4], mp 114.5–115℃, 96.5 mg (36 %).

Catalytic Reduction of ***18***. An MeOH solution (2 cm³) of **18** (196 mg) was reduced

with Pd on carbon at 15–25℃ to give 4,5-dimethoxy-2,7-dimethyltropone (**20**) [Found: C, 68.02; H, 7.21 %. Calcd for $C_{11}H_{14}O_3$: C, 68.02: H, 7.27 %. ^{1}H NMR δ =2.32(6H, s), 3.88(6H, s) and 7.38(2H, s). ^{13}C NMR δ =24.0, 58.8, 129.5, 143.6, 150.1, and 187.9], pale yellow needles, mp 48–50℃, 87.4 mg (84 %).

Catalytic Reduction of ***19***. Similarly, **19** (2.1 g) was reduced to 2,5-dimethoxy-4,6-dimethyltropone (**21**) [Found: M.W., 194.0941 (M^+); Calcd for $C_{11}H_{14}O_3$: M.W., 194.0941. ^{1}H NMR δ =2.31(3H, s), 2.37 (3H, s), 3.61(3H, s,), 3.86(3H, s), 6.55 (1H, s), and 7.14(1H, s). ^{13}C NMR δ = 21.7, 23.0, 56.0, 59.5, 116.1, 132.9, 135.8, 145.7, 155.9, 160.8 and 178.1], 433 mg (38.5 %), a colorless oil.

Hydrolysis of ***20***. An AcOH solution (0.5 cm^3) of **20** (25 mg) containing 48 %-HBr (0.5 cm^3) was heated to 95℃ for 10 h to give 4,6-dimethyltropolone (**17**), mp 192–193℃, quantitative yield.

*4,6-Dimethyl-*p*-tropoquinone* (***22***). An acetone solution (2 cm^3) of **17** (30 mg) was treated with DDQ(42.5 mg) gave 4,6-dimethyl-*p*-tropoquinone (**22**) [Found: 65.97; H, 4.87 %. Calcd for $C_9H_8O_3$: C, 65.85; H, 4.91 %. ^{1}H NMR δ =2.23(6H, d, J=1.5 Hz) and 6.75(2H,q, J=1.5 Hz). ^{13}C NMR δ =22.0(2C), 131.6(2C), 150.6 (2C), 186.0(2C), and 190.6], pale yellow needles, mp 54–56℃, 24.4 mg (82 %).

*Catalytic Hydrogenation of 3,6-(Diallyl)-5-hydroxytropolone(****23****)*[6]. An MeOH solution (3 cm^3) of **23** (30 mg) was treated with Pd on carbon under the H_2 atmosphere for 30 min to give 5-hydroxy-3,6-dipropyltropolone (**24**) [Found: C, 70.16; H, 8.15 %. Calcd for $C_{13}H_{18}O_3$: C, 70.24; H, 8.16 %. ^{1}H NMR(CD_3OD) δ =0.97(6H, t, J=7 Hz), 1.63(4H, m), 2.65(4H, td, J=8, 3 Hz), 7.33(2H, t, J=3 Hz). ^{13}C NMR (CD_3OD) δ =14.3(2C), 24.0(2C), 39.8(2C), 129.3(2C), 144.1(2C), 161.7(3C)], pale yellow needles, mp 147–149℃, 18.5 mg (61 %).

DDQ-dehydrogenation of ***23***. An acetone solution (2 cm^3) of **23** (20 mg) was treated with DDQ (32.4 mg) at room temperature for 0.5 h afforded 3, 6-diallyl-*p*-tropoquinone (**25**) [Found: C, 72.44; H, 5.66 %. Calcd for $C_{13}H_{12}O_3$: C, 72.21; H, 5.59 %. ^{1}H NMR δ =3.30(4H, dq, J=6.5, 1.2 Hz), 5.14(2H, ddt, J=16.5, 1.5, 1.2 Hz), 5.23(2H, ddt, J=10.5, 1.5, 1.2 Hz), 5.78(2H, ddt, J=16.5, 10.5, 6.5 Hz), and 6.64(2H, t, J=1.2 Hz). ^{13}C NMR δ =38.4 (2C), 119.9(2C), 130.7(2C), 132.5(2C), 153.1(2C), and 185.7(3C)], a pale yellow oil, 13 mg (66 %).

DDQ-dehydrogenation of ***24***. Similarly, an acetone solution (3 cm^3) of **24** (33 mg) was treated with DDQ (45 mg) to give 3,6-dipropyl-*p*-tropoquinone (**26**) [Found: C, 70.67; H, 7.40 %. Calcd for $C_{13}H_{16}O_3$: C, 70.89; H, 7.32 %. ^{1}H NMR δ =0.97(6H, t, J=7.5 Hz), 1.54(4H, m),2.56(4H, td, J=7.5, 1.2 Hz), and 6.60(2H, t, J= 1.2 Hz). ^{13}C NMR δ =13.7(2C), 21.6(2C), 37.1(2C), 130.0(2C), 155.8 (2C), 185.6 (2C), and 192.7], a pale yellow oil, 28.3 mg (87 %).

We wish to thank Mr. Kozo Tajiri, M. Eng., for the preliminary experiment on the Mannich reaction of 5-hydroxytropolone.

References

1) A. Kawamata, Y. Fukazawa, Y. Fujise, and S. Itô, *Tetrahedron Lett.*, **1982**, 1083.
2) H. Takeshita, T. Kusaba, and A. Mori, *Chem. Lett.*, **1983**, 1371.
3) H. Takeshita, T. Kusaba, and A. Mori, *Chem. Lett.*, **1982**, 701.
4) H. Takeshita, T. Kusaba, and A. Mori,

Bull. Chem. Soc. Jpn., **55**, 1659 (1982).
5) H. Takeshita and H. Mametsuka, *Chem. Lett.*, **1982**, 1061.
6) H. Takeshita, K. Tajiri, and I. Kouno, *Kyushu Daigaku Seisan Kagaku Kenkyusho Hokoku*, **70**, 65 (1979).
7) Detailed aspects of chemistry of the *p*-tropoquinone acetals will be a subject of an independent paper.
8) The NMR spectra were measured in $CDCl_3$ unless otherwise stated, by an FX 100 model spectrometer, JEOL, Tokyo, and the chemical shifts were expressed in δ unit from the internal Me_4Si.