Synthesis of 3-Oxosapriparaquinone, a Diterpene from *Salvia prionitis* Hance

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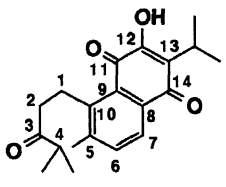
12-Acetoxy-5,10-*friedo*-4,5-*seco*-abieta-3,5(10),6,8,11,13-hexaene prepared from (+)-dehydroabietic acid, was converted into a natural rearranged abietane-type diterpene, 3-oxosapriparaquinone, via 12-benzoyloxy-3-hydroxy-5,10-*friedo*-4,5-*seco*-abieta-5(10),6,8,12-tetraene-11,14-dione by a series of reactions: hydroboration–oxidation, benzoyl peroxide oxidation, Jones oxidation, and alkaline hydrolysis.

3-Oxosapriparaquinone[1,2] (**1**), a rare 4,5-*seco*-abietane type diterpene possessing a rearranged angular methyl group, was isolated from the roots of *Salvia prionitis* Hance (*Labiatae*) which is used in Chinese folk medicine as an antiphlogistic, antibacterial, and antitubercular drug. Recently, we reported the rearrangement of the angular methyl group in dehydroabietic acid derivatives,[3] and the syntheses of two rare 5,10-*friedo*-4,5-*seco*-abietane diterpenes, saprorthoquinone (**2**) and 4-hydroxysapriparaquinone[4] (**3**) (Fig. 1). As an extension of the previous works, we now describe a synthesis of 3-oxosapriparaquinone (**1**).

According to our previous method,[4] 12-acetoxyabieta-5,8,11,13-tetraen-7-one (**4**) prepared from (+)-dehydroabietic acid was converted into 12-acetoxy-5,10-*friedo*-4,5-*seco*-abieta-3,5(10),6,8,11,13-hexaene[4] (**6**) via a 7-hydroxy compound (**5**). Hydroboration of **6** with borane–tetrahydrofuran complex and then treatment with alkaline hydrogen peroxide afforded a 3,12-diol (**7**) in 75.9% yield (Fig. 2). To introduce an oxygen function at the C-11 position, the diol **7** was refluxed with benzoyl peroxide[5] in dichloromethane. The crude product was purified by recrystallization and repeated column chromatography on silica gel to give two benzoates, **8** and **9**, in 16.1 and 56.5% yields. The mass spectrum of the minor benzoate **8** gave a molecular ion peak at m/z 540.2539 (M^+), corresponding to the formula $C_{34}H_{36}O_6$. The infrared (IR) spectrum showed absorption bands at 3550 and 3230 cm^{-1} due to a hydroxyl group, at 1730 cm^{-1} due to benzoyloxy groups, and at 1690 cm^{-1} due to an α,β-unsaturated carbonyl group. In the ^1H NMR spectrum, the compound **8** exhibited the presence of two isopropyl groups at δ=0.80 and 1.11 (each 6H, d, J=6.8 Hz), a methyl group on aryl ring at δ=2.42 (3H, s), an olefinic proton at δ=6.80 (1H, s), two ortho-coupling aromatic protons at δ=7.10 and 7.39 (each 1H, d, J=7.8 Hz), and ten aromatic protons of two benzoyloxy groups at δ=7.46 (4H, t, J=7.8 Hz), 7.61 (2H, t, J=7.8 Hz), and 8.09 (4H, d, J=7.8 Hz). In a previous paper,[5] we also reported that the ^1H NMR spectrum of 2,2-bis(benzoyloxy)-3-isopropyl-1(2H)-naphthalenone (**12**) indicated signals due to isopropyl methyls at δ=1.11 (6H, d, J=7.0 Hz) and a C-4 olefinic proton at δ=6.88 (1H, s), while that of 1,1-bis(benzoyloxy)-3-isopropyl-2(1H)-naphthalenone (**13**) indicated the corresponding signals at δ=1.27 (6H, d, J=7.0 Hz) and 7.23 (1H, s). From the comparisons of the chemical shifts of isopropyl methyls and an olefinic proton in **8** with those in **12** and **13**, the structure of **8** was assigned as 12,12-bis(benzoyloxy)-3-hydroxy-



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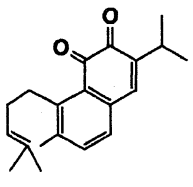

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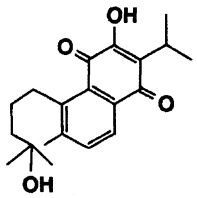

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Fig. 1.

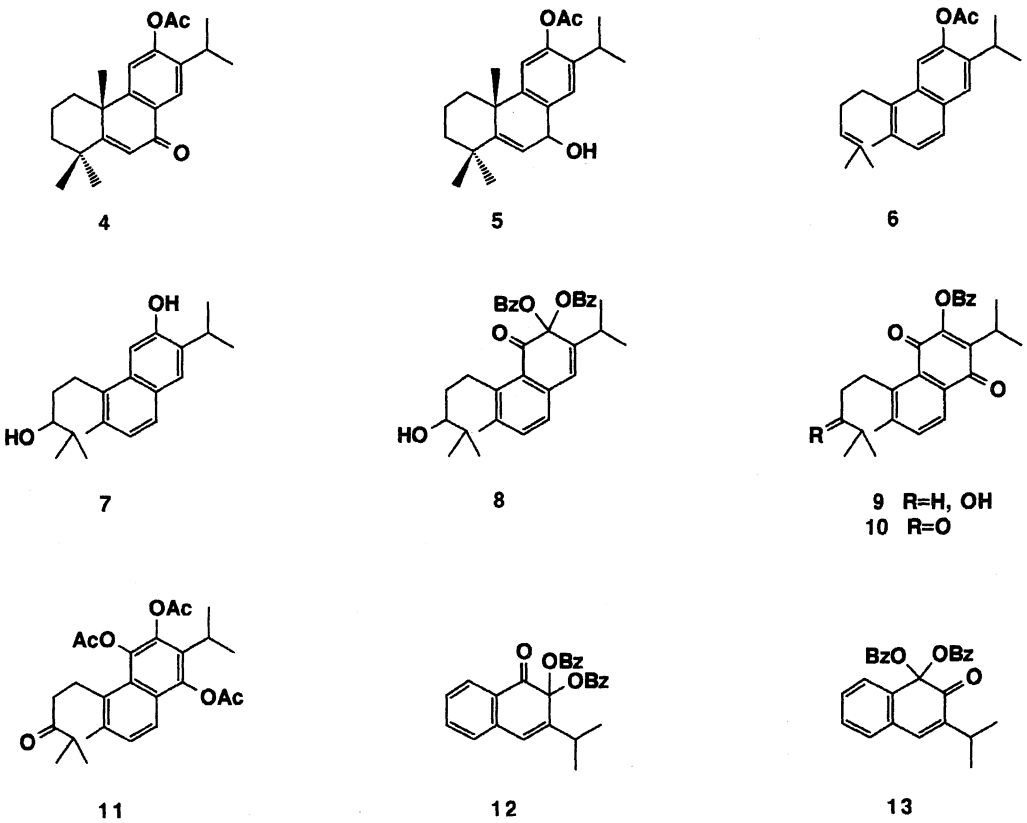


Fig. 2.

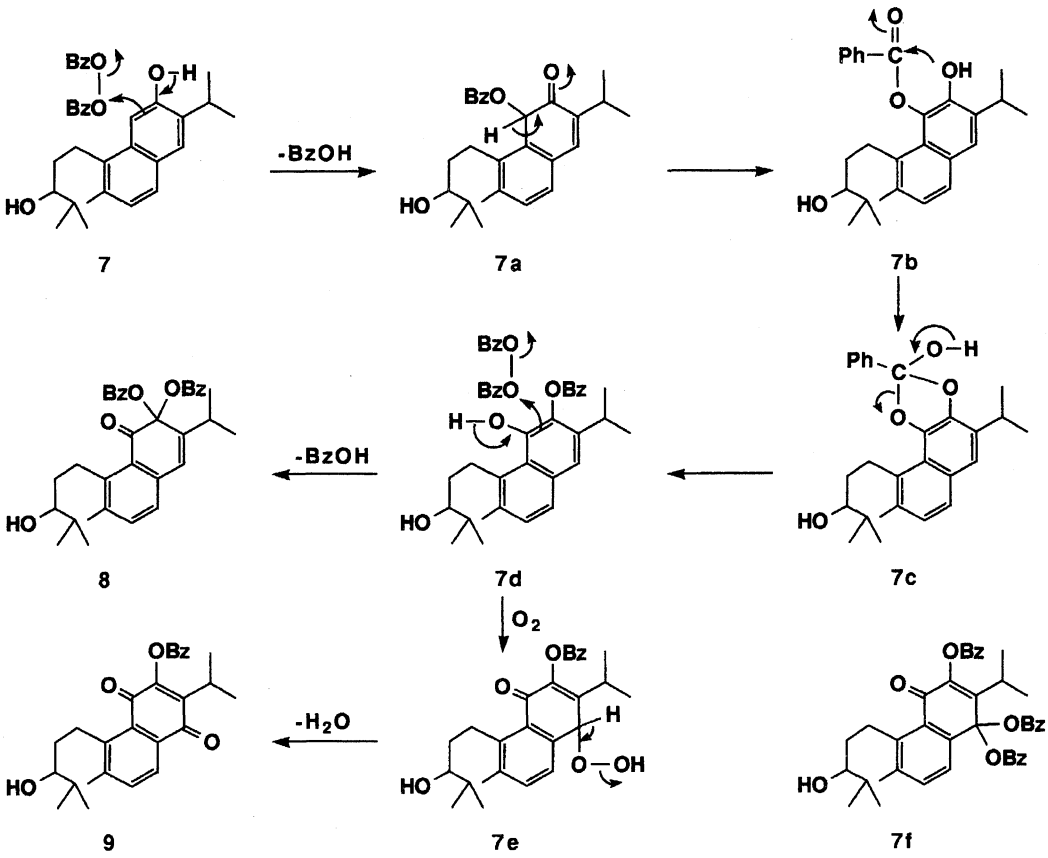
5,10-*friedo*-4,5-*seco*-abieta-5(10),6,8,13-tetraen-11-one. On the other hand, the mass spectrum of the major benzoate **9** gave a molecular ion peak at m/z 434.2067 (M^+), corresponding to the formula $C_{27}H_{30}O_5$. Its IR spectrum showed absorption bands at 3580 and 3250 cm^{-1} due to a hydroxyl group, at 1735 cm^{-1} due to a benzoyloxy group, and at 1660 cm^{-1} due to a *p*-quinone. The ^1H NMR spectrum of **9** exhibited the presence of two isopropyl groups at $\delta=0.90$ (6H, d, $J=6.5$ Hz) and 1.31 (6H, d, $J=7.0$ Hz), a methyl group on aryl ring at $\delta=2.47$ (3H, s), two ortho-coupling aromatic protons at $\delta=7.51$ and 7.99 (each 1H, d, $J=7.9$ Hz), and five aromatic protons of a benzoyloxy group at $\delta=7.44$—8.28 (5H, m). Appearance of a signal due to one of two ortho-coupling aromatic protons at very low field ($\delta=7.99$) suggested the presence of a *p*-quinone moiety. Thus, the structure of **9** was assigned as 12-benzoyloxy-3-hydroxy-5,10-*friedo*-4,5-*seco*-abieta-5(10),6,8,12-tetraene-11,14-dione.

Oxidation of **9** with Jones reagent in acetone, followed by hydrolysis of the resulting 3-oxo compound (**10**: 72.6% yield) with aqueous sodium hydrogencarbonate in refluxing methanol afforded the desired hydroxy *p*-quinone (**1**: 94.5% yield), which was shown to be identical with natural 3-oxosapriparaquinone by spectral comparisons. The synthetic **1** was further characterized as a triacetate (**11**) by reductive acetylation with refluxing acetic anhydride in the presence of zinc powder.

Probable mechanisms for the conversion of the 3,12-diol (**7**) into the benzoates, **8** and **9**, are depicted in Scheme 1. The diol **7** is first oxidized with benzoyl peroxide to a 11-benzoyloxy-12-oxo intermediate (**7a**) which is transformed into a 11-benzoyloxy-12-hydroxy compound (**7b**) by deprotonation at the C-11 position. Owing to the severe peri interaction between a benzoyloxy group at the C-11 position and a side chain at the C-10 position, the compound **7b** is rapidly isomerized into a 12-benzoyloxy-11-hydroxy compound (**7d**) via a cyclic intermediate (**7c**). Further oxidation of **7d** with benzoyl peroxide provides the 12,12-bis(benzoyloxy) compound (**8**). On the other hand, autoxidation of **7d** on silica gel column results in the formation of a hydroperoxide intermediate (**7e**) which is then transformed into the *p*-quinone (**9**) by dehydration. Another route leading to the *p*-quinone (**9**) also seems to be possible. Namely, the compound **7d** is oxidized with benzoyl peroxide at the para position of the C-11 hydroxyl group to give a 12,14,14-tribenzoyloxy intermediate (**7f**) which is hydrolyzed to the *p*-quinone (**9**) during the silica-gel column chromatography. However, the ^1H NMR spectrum of the crude oxidation product, after separation of **8** by crystallization, showed the presence of a monobenzoate (**7d**), but differed from that of a tribenzoate (**7f**). Therefore, this route is excluded.

Experimental

All melting points were determined on a Yanagimoto mi-



Scheme 1.

cro melting point apparatus and are uncorrected. The IR spectra were measured on a Shimadzu IR-400 spectrometer in chloroform. The mass spectra were recorded on a JEOL JMS-SX 102A spectrometer. The ^{1}H NMR spectra were recorded with a Hitachi R-1500 (60 MHz) or a JEOL JNM EX-400 (400 MHz) spectrometer in deuteriochloroform using tetramethylsilane as an internal standard unless otherwise stated. The following abbreviations are used: s=singlet, d=doublet, dd=double doublet, t=triplet, m=multiplet, br=broad. Column chromatography was performed using Merck silica gel (0.063—0.200 mm).

5,10-*Friedo*-4,5-*seco*-abieta-5(10),6,8,11,13-pentaene-3,12-diol (7). A solution of borane–tetrahydrofuran complex (1 mol dm^{-3}: 4.0 ml) was added dropwise to a stirred solution of 12-acetoxy-5,10-*friedo*-4,5-*seco*-abieta-3,5(10),6,8,11,13-hexaene[4] (**6**) (654 mg) in dry tetrahydrofuran (8.0 ml) at −15 to −6 °C for 1.5 min under a stream of nitrogen. After the mixture had been stirred at 0—5 °C for 3 h, the following solutions were added successively at −15 to −7 °C: aqueous tetrahydrofuran (50%, 1.8 ml), aqueous sodium hydroxide (12%, 1.8 ml), and hydrogen peroxide (30%, 1.8 ml). The mixture was stirred at −5 to 0 °C for 30 min and at room temperature for 1 h, then diluted with brine, and extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (50 g), using chloroform as an eluent, to give a diol (**7**) (460 mg: 75.9% yield). This was recrystallized from a mixture of acetone and hexane, mp 124—125 °C, IR 3580 and 3375 cm^{-1}. ^{1}H NMR (60 MHz) δ=0.93 (6H, d, J=6.5 Hz, –CH(C$\underline{H}_3$)$_2$), 1.34 (6H, d, J=6.7 Hz, –CH(C$\underline{H}_3$)$_2$), 1.57—2.23 (4H, m, C2–H$_2$, C3–OH, and C4–H), 2.46 (3H, s, –CH$_3$), ca. 2.7—3.7 (4H, m, C1–H$_2$, C3–H, and C15–H), 6.28 (1H, s, C12–OH), 7.10 and 7.52 (each 1H, d, J=8.2 Hz, C6–H and C7–H), 7.38 and 7.58 (each 1H, s, C11–H and C14–H). Found: C, 79.73; H, 9.52%; HRMS m/z 300.2097 (M$^+$). Calcd for $C_{20}H_{28}O_2$: C, 79.95; H, 9.39%; M, 300.2089.

12,12-Bis(benzoyloxy)-3-hydroxy-5,10-*friedo*-4,5-*seco*-abieta-5(10),6,8,13-tetraen-11-one (8) and 12-Benzoyloxy-3-hydroxy-5,10-*friedo*-4,5-*seco*-abieta-5(10),6,8,12-tetraene-11,14-dione (9). A solution of **7** (398 mg) and benzoyl peroxide (428 mg) in dichloromethane (18 ml) was gently refluxed for 2 h. After the addition of ether (30 ml), acetic acid (0.4 ml), and aqueous potassium iodide (10%, 10 ml), the mixture was stirred at room temperature for 1 h and then washed successively with water, aqueous sodium thiosulfate, aqueous sodium hydrogencarbonate, and brine. The dried solution was evaporated in vacuo. The residue was recrystallized from a mixture of acetone and hexane to give **8** (115 mg: 16.1% yield), mp 188—189 °C. IR 3550, 3230, 1730, and 1690 cm^{-1}. ^{1}H NMR (400 MHz) δ=0.798 and 0.804 (each 3H, d, J=6.8 Hz, –CH(C$\underline{H}_3$)$_2$), 1.11 (6H, d, J=6.8 Hz, –CH(C$\underline{H}_3$)$_2$), 1.25 (1H, s, –OH), 1.45—1.72 (3H, m, C2–H$_2$ and C4–H), 2.42 (3H, s, –CH$_3$), 2.89 (1H, m, J=6.8 Hz, –C$\underline{H}$(CH$_3$)$_2$), 3.21—3.45 (3H, m, C1–H$_2$ and C3–H), 6.80 (1H, s, C14–H), 7.10 and 7.39 (each 1H, d, J=7.8 Hz, C6–H and C7–H), 7.46 (4H, t, J=7.8 Hz), 7.61 (2H, t, J=7.8 Hz), and 8.09 (4H, d, J=7.8 Hz) (2-OCOC$_6$H$_5$). Found: C, 75.67; H, 6.66%; HRMS m/z 540.2539 (M$^+$). Calcd for $C_{34}H_{36}O_6$: C, 75.53; H, 6.71%;

M, 540.2512.

The mother liquor of the above recrystallization was evaporated in vacuo. The residue was purified by repeated column chromatography on silica gel (50—100 times the sample weight in each case), using chloroform as an eluent, to give a *p*-quinone (**9**) as an oil (326 mg: 56.5% yield). IR 3580, 3250, 1735, and 1660 cm^{-1}. ^1H NMR (60 MHz) δ=0.90 (6H, d, J=6.5 Hz) and 1.31 (6H, d, J=7.0 Hz) (2-CH($C\underline{H}_3$)$_2$), ca. 1.4—2.3 (4H, m, overlap, C2–H_2, C3–OH, and C4–H), 2.47 (3H, s, –CH_3), ca. 3.0—3.6 (4H, m, C1–H_2, C3–H, and C15–H), 7.51 and 7.99 (each 1H, d, J=7.9 Hz, C6–H and C7–H), 7.44—8.28 (5H, m, –$OCOC_6H_5$). HRMS Found: m/z 434.2067 (M^+). Calcd for $C_{27}H_{30}O_5$: M, 434.2093. Further elution with ether–chloroform (15 : 85) afforded the recovered **7** (53 mg).

12-Benzoyloxy-5,10-*friedo*-4,5-*seco*-abieta-5(10),6,8,12-tetraene-3,11,14-trione (10). Jones reagent (1.0 mol dm^{-3}, 0.15 ml) was added to a stirred solution of **9** (62 mg) in acetone (1.0 ml) with cooling in an ice-water bath over a period of 2 min. After stirring at this temperature for 2 min, the mixture was diluted with ether and washed with brine. The dried solution was evaporated in vacuo. The residue was chromatographed on silica gel (10 g), using hexane–chloroform (3 : 7) as an eluent, to give a trione (**10**) as an oil (45 mg: 72.6% yield). IR 1735, 1705, and 1660 cm^{-1}. ^1H NMR (60 MHz) δ=1.07 and 1.31 (each 6H, d, J=6.7 Hz, 2-CH($C\underline{H}_3$)$_2$), 2.4—2.9 (3H, m, C2–H_2 and C4–H), 2.45 (3H, s, –CH_3), 3.15—3.60 (3H, m, C1–H_2 and C15–H), 7.52 and 8.00 (each 1H, d, J=7.9 Hz, C6–H and C7–H), 7.45—8.28 (5H, m, –$OCOC_6H_5$). HRMS Found: m/z 432.1917 (M^+). Calcd for $C_{27}H_{28}O_5$: M, 432.1937.

3-Oxosapriparaquinone (1). A mixture of **10** (53 mg) and aqueous sodium hydrogencarbonate (5%, 3.2 ml) in methanol (13 ml) was refluxed for 1 h. After removal of the methanol in vacuo, the residue was acidified with dilute hydrochloric acid, refluxed for 30 min, and then extracted with ether. The ether extract was washed with brine, dried over sodium sulfate, and evaporated in vacuo. The residue was chromatographed on silica gel (10 g), using hexane–chloroform (3 : 7) as an eluent, to give a hydroxy *p*-quinone (**1**) (38 mg: 94.5% yield) which was recrystallized from hexane to give yellow needles, mp 108—109 °C. IR 3370, 1710, and 1645 cm^{-1}. ^1H NMR (60 MHz) δ=1.16 and 1.29 (each 6H, d, J=7.0 Hz, 2-CH($C\underline{H}_3$)$_2$), 2.43 (3H, s, –CH_3), 2.63 (3H, m, C2–H_2 and C4–H), 3.39 (3H, m, C1–H_2 and C15–H), 7.52 (1H, d, J=7.9 Hz, C6–H), 7.70 (1H, s, –OH), 8.00 (1H, d, J=7.9 Hz, C7–H). Found: C, 73.28; H, 7.29%; HRMS m/z 328.1692 (M^+). Calcd for $C_{20}H_{24}O_4$: C, 73.14; H, 7.37%; M, 328.1675. The synthetic **1** was shown to be identical with natural 3-oxosapriparaquinone (mp 102 °C[1)]) by spectral comparisons.

11,12,14-Triacetoxy-5,10-*friedo*-4,5-*seco*-abieta-5(10),6,8,11,13-pentaen-3-one (11). A stirred mixture of the synthetic **1** (22 mg) and zinc powder (100 mg) in acetic anhydride (2.0 ml) was refluxed for 2 h. The mixture was filtered and the filtrate was evaporated in vacuo. The residue was chromatographed on silica gel (10 g), using chloroform as an eluent, to give a triacetate (**11**) as an oil (22 mg: 71.9% yield), IR 1760 and 1705 cm^{-1}. ^1H NMR (60 MHz) δ=1.11 and 1.29 (each 6H, d, J=7.0 Hz, 2-CH($C\underline{H}_3$)$_2$), 2.2—3.0 (3H, m, overlap, C2–H_2 and C4–H), 2.31, 2.33, 2.44, and 2.47 (each 3H, s, 3-$OCOCH_3$ and –CH_3), 3.1—3.5 (3H, m, C1–H_2 and C15–H), 7.25 and 7.49 (each 1H, d, J=8.6 Hz, C6–H and C7–H). HRMS Found: m/z 456.2137 (M^+). Calcd for $C_{26}H_{32}O_7$: M, 456.2148.

References

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2) Although the natural compound was originally named 3-ketosapriparaquinone,[1)] we suggest a more favorable name, 3-oxosapriparaquinone, for the natural compound, and this name is adopted in this paper.

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