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Lactones of Hydrogenated 5,8-Dihydroxy-4-methylnaphthalene-1-carboxylic Acids

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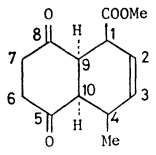
Synopsis. The γ- and δ-lactones were derived from the Diels-Alder adduct of *p*-benzoquinone and methyl sorbate.

Generally, whether a γ- or δ-lactone is formed in a reaction depends mainly on the stability of the lactone under the reaction conditions.[1] This paper deals with the lactones of *cis*-octahydro- and *cis*-decahydro-5β,8β-dihydroxy-4β-methylnaphthalene-1β-carboxylic acids.

The Diels-Alder adduct[2] of *p*-benzoquinone and methyl sorbate was reduced with zinc to **1**, which was hydrogenated to **2a** in the presence of palladium-carbon, and to **3a** with platinum oxide. Lactonization of **3a** in methanolic hydrogen chloride afforded the keto δ-lactone (**4**), supporting the cis ring junctions in **1**, **2a**, and **3a**.



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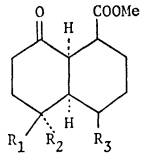

2a R_1,R_2=O R_3=Me
2b R_1,R_2=O R_3=H
3a R_1=OH R_2=H R_3=Me
3b R_1=OH R_2,R_3=H

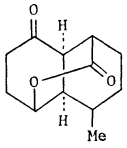

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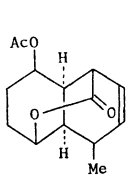
Fig. 1.

The reduction of **1** with sodium borohydride followed by treatment with acetic anhydride and pyridine gave the acetoxy δ-lactone (**5**) and the $\Delta^{1,2}$-γ-lactone (**6**), the latter of which afforded the acetate (**7**) by acetylation at elevated temperature. Treatment of **5** with sodium methoxide gave **6**. An attempt to convert **6** into the corresponding saturated γ-lactone (**8a**) by catalytic hydrogenation with platinum oxide failed, but gave the δ-lactone (**9**) and the $\Delta^{1,9}$-γ-lactone (**10**). The δ-lactone **9**, which was stable against treatment with sodium methoxide, was obtained from **2a** or **3a** by sodium borohydride reduction, or from **4** by hydrogenation under the similar conditions to those in the preparation of **3a**. The C-8 carbonyl group of **4** is obviously less hindered than that of **3a**.

On the other hand, Wheeler *et al.* reported the reduction of **2b** under Meerwein-Ponndorf conditions to **8b**, which was also obtained from **8c** by catalytic hydrogenation or sodium borohydride reduction.[3,4]

It is interesting to infer the conformations of **2a** and **3a**. The signal for the equatorial proton on C-5 (CH–O–) in the ^{1}H NMR spectrum of **4** appears at 4.95 ppm as a broad singlet (W_H=7 Hz), while a multiplet signal at 4.40 ppm (W_H=17 Hz) in the spectrum of **3a** must be attributed to the axial proton on C-5 (CH–OH). The



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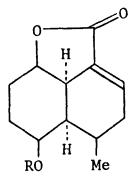
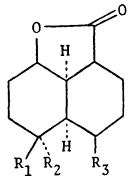
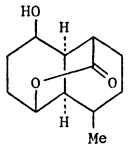


6 R=H
7 R=Ac



8a R_1=OH R_2=H R_3=Me
8b R_1=OH R_2,R_3=H
8c R_1,R_2=O R_3=H



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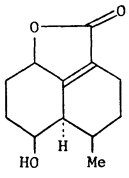

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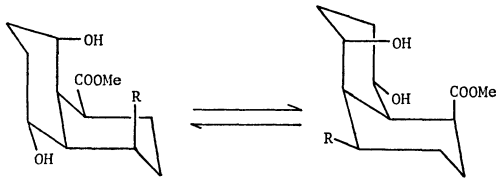
Fig. 2.

signals for C-1 in the ^{13}C NMR spectra of **3a** and **3b** appear at nearly the same fields. The signals for C-2 and -9 in **3a** are observed at fields higher than those of the corresponding carbons in **3b** as a consequence of the γ gauche effect of the methyl group. The similar shielding trends are also found for C-1, -2, and -9 in the spectra of **2a** and **2b**. These data indicate that **2a** and **3a** exist predominantly in the conformations similar to those of **2b** and **3b** which bear the equatorial methoxycarbonyl groups. Details will be published elsewhere.

Therefore, the conformations of the intermediate diol esters from **2a** and **2b** might affect the way of lactonization. The formation of **8b** seems to proceed through the preferred conformer **A** (R=H) similar to those of **2b** and **3b**. In the case of R=Me, **9** might be formed *via* the stable conformer **B**, since **A** is unstable on account of the steric effect of the methyl group.



A B

Fig. 3.

Experimental

Melting points are uncorrected. The IR spectra were recorded on a Hitachi Infrared Spectrometer EPI-G_3 in

nujol, unless otherwise noted. The UV spectra were recorded on a Shimadzu MPS-50L in EtOH. The ^1H and ^{13}C NMR spectra were obtained on a JNM-PS-100 or JNM-PFT-60 in $CDCl_3$. Chemical shifts are given in δ-values with respect to TMS as an internal standard. Assignment of chemical shifts for close-lying peaks marked with asterisk may be reversed. Compounds **2b** and **3b** were prepared according to literature procedures.[5]

Preparation of ***1***. A solution of 18.0 g of *p*-benzoquinone and 17.6 g of methyl sorbate in 150 ml of benzene was refluxed for 19 h, and concentrated *in vacuo*. The residue was treated with 50 g of zinc in 150 ml of AcOH at room temperature for 2 h to give 2.30 g of the unreduced adduct[2] and 6.95 g of **1**: mp 136—137 °C (from EtOH); IR 1735 and 1702 cm^{-1}; ^1H NMR 0.88 (3H, d, J=7 Hz, CMe), 2.4—3.4 (7H), 3.71 (3H, s, OMe), *ca.* 3.8 (1H, m), 5.65 (1H, m, -CH=), and 6.04 ppm (1H, br d, J=11 Hz, -CH=); ^{13}C NMR 17.04 (CMe), 30.55 (C-4), 34.73 (C-6), 37.61 (C-7), 39.44 (C-1), 46.05 (C-9), 48.33 (C-10), 52.10 (OMe), 121.37 (C-2), 131.27 (C-3), 172.06 (COO), 207.85 (C-5*), and 210.29 ppm (C-8*). Found: C, 66.19; H, 6.86%. Calcd for $C_{13}H_{16}O_4$: C, 66.08; H, 6.83%.

Preparation of ***2a***. Hydrogenation of 2.84 g of **1** with 266 mg of 5% Pd-C in 120 ml of MeOH gave 2.51 g of **2a**: mp 110—111 °C (from EtOH); IR 1721 and 1706 cm^{-1}; ^1H NMR 0.84 (3H, d, J=7 Hz, CMe), 1.4—3.1 (11H), *ca.* 3.5 (1H, m), and 3.69 ppm (3H, s, OMe); ^{13}C NMR 15.82 (CMe), 20.08 (C-2), 30.47 (C-3), 31.45 (C-4), 35.10 (C-6), 37.41 (C-7), 41.35 (C-1), 47.68 (C-9), 51.13 (C-10), 51.78 (OMe), 173.52 (COO), 208.91 (C-5*), and 209.80 ppm (C-8*). Found: C, 65.32; H, 7.68%. Calcd for $C_{13}H_{18}O_4$: C, 65.53; H, 7.61%.

^{13}C NMR of ***2b***. 23.49 (C-3*), 23.98 (C-2*), 26.62 (C-4), 35.83 (C-6), 36.56 (C-7), 41.23 (C-1), 48.41 (C-10), 49.22 (C-9), 51.82 (OMe), 173.60 (COO), 207.85 (C-8*), and 209.56 ppm (C-5*).

Preparation of ***3a***. Hydrogenation of 2.92 g of **1** with 95 mg of PtO_2 in 120 ml of MeOH gave 2.33 g of **3a**: mp 124—125 °C (from benzene); IR 3370, 1744, and 1693 cm^{-1}; ^1H NMR 0.97 (3H, d, J=7 Hz, CMe), 1.3—2.8 (12H), 3.18 (1H, br t, J=5 Hz), 3.65 (3H, s, OMe), and 4.40 ppm (1H, m, W_H=17 Hz, C<u>H</u>-OH); ^{13}C NMR 17.12 (CMe), 19.55 (C-2), 27.67 (C-4), 31.61 (C-6), 34.04 (C-3), 37.90 (C-7), 42.69 (C-1), 47.27 (C-9*), 47.56 (C-10*), 51.61 (OMe), 70.20 (C-5), 174.57 (COO), and 210.94 ppm (C-8). Found: C, 64.97; H, 8.65%. Calcd for $C_{13}H_{20}O_4$: C, 64.98; H, 8.39%.

^{13}C NMR of ***3b***. 21.18 (C-4), 23.98 (C-2*), 24.83 (C-3*), 29.21 (C-6), 38.51 (C-7), 42.56 (C-1), 45.69 (C-10), 49.75 (C-9), 51.70 (OMe), 70.45 (C-5), 174.57 (COO), and 209.48 ppm (C-8).

Lactonization of ***3a*** *to* ***4***. Treatment of 160 mg of **3a** with 5 ml of 6% methanolic hydrogen chloride at 20 °C overnight gave 101 mg of **4**: mp 100—101 °C (from benzene–hexane); IR 1733 and 1712 cm^{-1}; ^1H NMR 1.14 (3H, d, J=6 Hz, CMe), 1.3—2.9 (12H), and 4.95 ppm (1H, br s W_H=7 Hz, CH-O-). Found: C, 69.18; H, 7.91%. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%.

$NaBH_4$ Reduction of ***1*** *and Subsequent Acetylation*. Reduction of 1.69 g of **1** with 0.8 g of $NaBH_4$ in 80 ml of MeOH at 0 °C for 1.5 h gave an oily product, which was treated with 7 ml of Ac_2O and 10 ml of pyridine at room temperature overnight to afforded 527 mg of **5** and 356 mg of **6**. **5**: mp 114—116 °C (from benzene–hexane); IR 1733 and 1252 cm^{-1}; ^1H NMR 1.21 (3H, d, J=7 Hz, CMe), 1.5—2.9 (7H), 2.08 (3H, s, OAc), 3.25 (1H, m, W_H=10 Hz, CH-COO), 4.76 (1H, br s, W_H=8 Hz, CH-O-), 4.98 (1H, m, W_H=18 Hz, C<u>H</u>-OAc), 5.70 (1H, dd, J=10 and 3 Hz, -CH=), and 5.93 ppm (1H, m, -CH=). Found: C, 67.26; H, 7.35%. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%. **6**: mp 155—157 °C (from EtOH); IR ($CHCl_3$) 3600, 3480, 1754, and 1691 cm^{-1}; UV max 225 nm (ε 8500); ^1H NMR 1.23 (3H, d, J=6 Hz, CMe), 1.3—2.6 (9H), 3.05 (1H, m), 4.23 (1H, br s, W_H= 13 Hz, C<u>H</u>-OH), 4.70 (1H, m, W_H=14 Hz, CH-O-), and 6.85 ppm (1H, q, J=6 and 3 Hz, -CH=). Found: C, 69.37; H, 7.84%. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%.

The Acetate ***7***. Treatment of 257 mg of **6** with 5 ml of Ac_2O and 7 ml of pyridine at 100—105 °C for 6 h gave 177 mg of **7**: mp 138—139 °C (from benzene–hexane); IR 1760, 1733, 1689, and 1250 cm^{-1}; UV max 222 nm (ε 9700); ^1H NMR 1.09 (3H, d, J=6 Hz, CMe), 1.2—2.7 (8H), 1.97 (3H, s, OAc), 3.15 (1H, m), 4.77 (1H, m, W_H=14 Hz, CH-O-), 5.25 (1H, br s, W_H=8 Hz, CH-OAc), and 6.90 ppm (1H, br d, J=3 Hz, -CH=). Found: C, 67.01; H, 7.25%. Calcd for $C_{14}H_{18}O_4$: C, 67.18; H, 7.25%.

Conversion of ***5*** *into* ***6***. Treatment of 99 mg of **5** with 3 ml of 1 M NaOMe at room temperature overnight gave 41 mg of **6**.

Catalytic Hydrogenation of ***6***. Hydrogenation of 343 mg of **6** with 36 mg of PtO_2 in 50 ml of AcOEt gave 125 mg of **9** and 142 mg of **10**. **9**: mp 105—106 °C (from benzene–hexane); IR ($CHCl_3$) 3600, 3430, and 1725 cm^{-1}; ^1H NMR 1.08 (3H, d, J=6 Hz, CMe), 1.3—2.4 (11H), 2.95 (2H, br s, W_H=9 Hz, O<u>H</u> and C<u>H</u>-COO), 3.80 (1H, m, W_H=17 Hz, C<u>H</u>-OH), and 4.70 ppm (1H, br s, W_H=8 Hz, CH-O-). Found: C, 68.42; H, 8.82%. Calcd for $C_{12}H_{18}O_3$: C, 68.54; H, 8.63%. **9** was stable against teratment with 1 M NaOMe at room temperature overnight. **10**: mp 181—182 °C (from benzene); IR ($CHCl_3$) 3600, 3470, 1750, and 1696 cm^{-1}; UV max 223 nm (ε 12500); ^1H NMR 1.21 (3H, d, J=6 Hz, CMe), 1.3—2.6 (11H), 4.30 (1H, m, W_H=12 Hz, C<u>H</u>-OH), and 4.70 ppm (1H, m, W_H=15 Hz, CH-O-). Found: C, 69.34; H, 7.71%. Calcd for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74%.

$NaBH_4$ Reduction of ***2a***. Reduction of 1.56 g of **2a** with 0.7 g of $NaBH_4$ in 50 ml of MeOH at 0 °C for 2 h gave 1.07 g of **9**. In a similar way, **9** was obtained from **3a** (204 mg from 323 mg of **3a**).

Catalytic Hydrogenation of ***4***. Hydrogenation of 81 mg of **4** with 2 mg of PtO_2 in 20 ml of MeOH gave 75 mg of **9**.

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