Novel Transformation of Formyl Groups into Hydroxyl Groups Utilizing Deformylative Autoxidation of Aldehydes

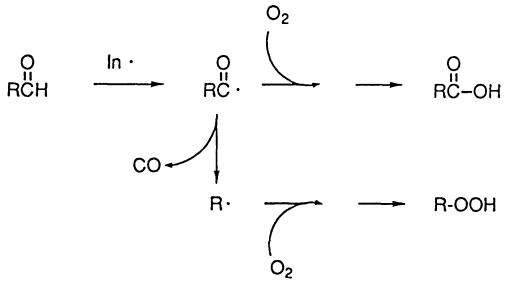
Hideo KIGOSHI, Yoshifumi IMAMURA, Akihiko SAWADA,
Haruki NIWA, and Kiyoyuki YAMADA*
Department of Chemistry, Faculty of Science, Nagoya University, Chikusa, Nagoya 464
(Received June 24, 1991)

Synopsis. Structural requirements that cause deformylative autoxidation of aliphatic aldehydes are investigated. Decarbonylation of acyl radicals proceeds smoothly when the alkyl radicals that are formed can be stabilized by allylic conjugation. Further conjugation of the double bond in the allyl radical with a carbonyl or a cyclopropyl group allows position-selective peroxidation of the alkyl radical.

In the course of the synthetic study on ptaquilosin (**2**), the aglycone of ptaquiloside (**1**) which is a bracken carcinogen, we encountered a necessity to convert an angular formyl group into the hydroxyl group efficiently. After unsuccessful trials, we found that autoxidation of **3** smoothly proceeded with deformylation to give hydroperoxide **4a**, reduction of which gave the desired alcohol **4b** in very high yield (Eq. 1). This novel transformation was applied to aldehydes **5** and **7**, culminating in the total synthesis of racemic ptaquilosin (**2**)[1] and (+)-ptaquilosin (**8b**) (the enantiomer of **2**)[2] via **6a** and **8a**, respectively (Eq. 2, 3). Herein we disclose the experimental details of deformylative hydroxylation of the aldehydes as well as the study on structural requirements causing deformylative autoxidation of aldehydes.

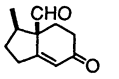
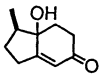
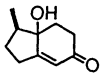
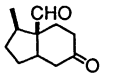
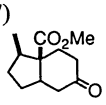
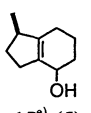
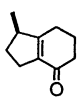
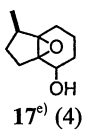
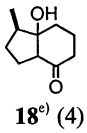
We have chosen aldehydes **9**, **10**, and **11** as the substrates suitable for the study on deformylative autoxidation (Table 1). Autoxidation of **3**, **5**, **7**, **9**, **10**, and **11** was performed in a concentrated ethyl acetate solution under oxygen (1 atm) at 40—65 °C. The resulting peroxides were reduced with Ph_3P and the crude products were purified chromatographically. The results are summarized in Table 1.

In general, autoxidation of aldehydes provides carboxylic acids through peroxidation of acyl radical intermediates. However, acyl radicals are also known to fragment with loss of carbon monoxide to generate alkyl radicals (Scheme 1).[3] If the rate of decarbonylation of



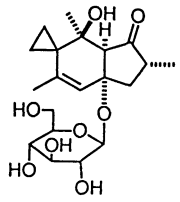
Scheme 1. Autoxidation of aldehydes.

Table 1. Deformylative Hydroxylation of Aldehydes

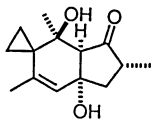
Entry	Substrate	Conditions temp (°C)/time (h)	Product (%)[a]
1	**3**	40/5	**4b** (92)
2	**5**	45/3.5	**6b** (89)
3	**7**[b]	50/18	**8b** (37)
4	 **9**[b]	65/23	 **12**[c] (17)  **13**[c] (20)
5	 **10**[b]	65/23	 **14**[d] (25)
6	 **11**[b]	65/23	 **15**[e] (5)  **16** (5)  **17**[e] (4)  **18**[e] (4)

a) Isolated yields after treatment with Ph_3P. b) This substrate afforded a complex mixture in this reaction, and ill-defined polar compounds were obtained as the major products. c) Stereochemistry of this compound was not determined. d) The carboxylic acid was isolated as methyl ester **14**. e) A mixture of diastereomers.

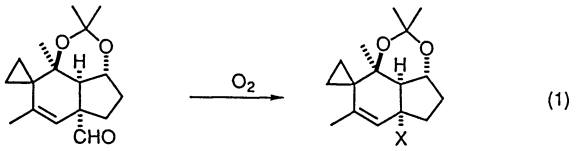
acyl radicals is faster than that of peroxidation of those, deformylative peroxidation becomes a predominant process in autoxidation of aldehydes. The ease of decarbonylation of acyl radicals may depend on stability of the alkyl radicals that are formed. In autoxidation of **3**, **5**, **7**, **9**, and **11** the facile decarbonylation occurs, being attributable to stabilization of the fragmented alkyl radical by allylic conjugation with the adjacent double bond (Entries 1—4 and 6). Autoxidation of **10**, which lacks structural features stabilizing the fragmented alkyl radical, proceeds without fragmentation to give the corresponding carboxylic acid (Entry 5). Peroxidation of the alkyl radicals generated from **3**, **5**, **7**, and **9**, proceeded in the position-selective manners, while peroxidation of the alkyl radical derived from **11** is nonselective.



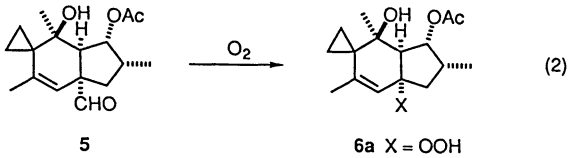
ptaquiloside (**1**)



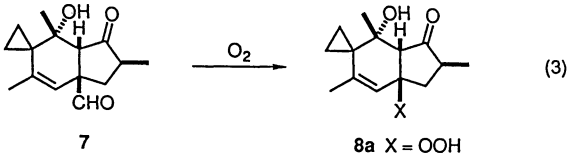
ptaquilosin (**2**)



3 **4a** X = OOH **4b** X = OH (1)



5 **6a** X = OOH **6b** X = OH (2)



7 **8a** X = OOH **8b** X = OH (3)

Experimental

Melting points are uncorrected. Optical rotations were measured on a JASCO DIP-181 polarimeter. Infrared (IR) spectra were obtained on a JASCO Model IR-810 spectrophotometer. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on a JEOL JNM-C675 (270 MHz) spectrometer in $CDCl_3$ or C_6D_6 using tetramethylsilane (TMS) as an internal standard. Chemical shifts are expressed in parts per million (ppm) downfield from TMS (δ=0.0) and coupling constants in Hz. The low-resolution (EIMS) and high-resolution (HREIMS) mass spectra were recorded on a JEOL JMS-LG2000 instrument. Fuji-Davison silica gel BW-820MH was used for column chromatography. Merck precoated silica gel 60 F_{254} plates, 0.25 mm thickness, were used for analytical and preparative thin-layer chromatography (TLC).

Preparation of (3′*R,3′a*R**,4′*S**,7′a*R**)-1′,2′,3′,3′a,4′,7′a-Hexahydro-3′,4′-dihydroxy-4′,6′-dimethyl-spiro[cyclopropane-1,5′-[5*H*]indene]-7′a-carbaldehyde Acetonide (3).** Compound **3** was prepared from compound **A**[1] by a three-step sequence [(1) CH_2=C(OCH_3)CH_3, H^+, benzene; (2) Bu_4NF, THF; (3) $CrO_3 \cdot 2Py$, CH_2Cl_2].

3: Colorless solids; IR (CCl_4) 2810, 2710, and 1725 cm^{-1}; ^{1}H NMR (C_6D_6, 270 MHz) δ=0.30—0.37 (1H, m), 0.62—0.77 (2H, m), 1.02—1.15 (1H, m), 1.20 (3H, d, *J*=1.7 Hz), 1.30 (3H, s), 1.31—1.38 (1H, m), 1.40 (3H, s), 1.53 (3H, d, *J*=0.7 Hz) 1.55—1.63 (1H, m), 1.79—1.91 (2H, m), 2.84 (1H, d, *J*=11.2 Hz), 4.12 (1H, ddd, *J*=11.2, 11.2, 5.6 Hz), 5.10 (1H, br s), and 9.23 (1H, s); EIMS *m/z* (rel intensity) 276 (M^+, 3), 218 (20), and 189 (100). HREIMS. Found: *m/z* 276.1752. Calcd for $C_{17}H_{24}O_3$: M, 276.1725.

Autoxidation of 3. A solution of **3** (3.9 mg, 0.014 mmol) in EtOAc (0.05 ml) was stirred under oxygen (1 atm) at 40 °C for 5 h. After the reaction mixture was diluted with ether (0.2 ml), Ph_3P (18 mg, 0.069 mmol) was added. The mixture was stirred at room temperature for 1 h and concentrated under reduced pressure. The residue was purified by column chromatography on silica gel [1 g, hexane–ether (5 : 1→1 : 1)] to give **4b** (3.4 mg, 92%) as colorless crystals: Mp 166.0—167.5 °C (hexane); IR (KBr) 3400, 3200, and 1660 cm^{-1}; ^{1}H NMR (C_6D_6, 270 MHz) δ=0.29—0.40 (2H, m), 0.66—0.80 (2H, m), 1.21 (3H, d, *J*=1.5 Hz), 1.41 (6H, s), 1.49 (3H, d, *J*=0.7 Hz), 1.51—1.63 (2H, m), 1.77—1.93 (3H, m), 2.54 (1H, d, *J*=11.6 Hz), 3.97 (1H, ddd, *J*=11.6, 10.1, 5.6 Hz), and 5.32 (1H, br s); EIMS *m/z* (rel intensity) 264 (M^+, 0.1), 246 (8), 231 (14), 206 (96), 191 (47), and 177 (100). HREIMS. Found: *m/z* 264.1745. Calcd for $C_{16}H_{24}O_3$: M, 264.1726.

Autoxidation of (2′*R,3′*R**,3′a*R**,4′*S**,7′a*R**)-3′-(Acetoxy)-1′,2′,3′,3′a,4′,7′a-hexahydro-4′-hydroxy-2′,4′,6′-trimethyl-spiro[cyclopropane-1,5′-[5*H*]indene]-7′a-carbaldehyde (5).** Autoxidation of **5**[1] (4.0 mg, 0.014 mmol) at 45 °C for 3.5 h and subsequent treatment with Ph_3P were performed as described above. The crude product was purified by column chromatography on silica gel [1 g, hexane–EtOAc (2 : 1)] to give racemic **6b** (3.5 mg, 89%) as a colorless oil. HREIMS. Found: *m/z* 280.1681. Calcd for $C_{16}H_{24}O_4$: M, 280.1675. Spectral properties of racemic **6b** were identical with those of authentic **6b**[4] derived from natural ptaquiloside (**1**), in all respects.

Autoxidation of (2′*S*,3′a*R*,4′*R*,7′a*S*)-1′,2′,3′,3′a,4′,7′a-Hexahydro-4′-hydroxy-2′,4′,6′-trimethyl-3′-oxo-spiro[cyclopropane-1,5′-[5*H*]indene]-7′a-carbaldehyde (7). Autoxidation of **7**[2] (8.3 mg, 0.033 mmol) at 50 °C for 18 h and subsequent treatment with Ph_3P were performed as described above. The crude product was purified by column chromatography on silica gel [1.5 g, hexane–ether (2 : 1→1 : 1)] to give (+)-ptaquilosin (**8b**) [2.9 mg, 37%, $[\alpha]_D^{20}$ +232° (*c* 0.17, $CHCl_3$) as a colorless oil. HREIMS. Found: *m/z* 236.1418. Calcd for $C_{14}H_{28}O_3$: M, 236.1412. Spectral properties of (+)-**8b** were identical with those of authentic (−)-ptaquilosin (**2**)[4] [$[\alpha]_D^{20}$ −246° (*c* 0.824, $CHCl_3$)] derived from natural ptaquiloside (**1**), in all respects.

Preparation of (3*R*,3a*R*)-1,2,3,4,5,6-Hexahydro-3-methyl-6-oxo-3a*H*-indene-3a-carbaldehyde (9), (3*R*,3a*R*,7a*S*)-Octahydro-3-methyl-6-oxo-3a*H*-indene-3a-carbaldehyde (10), and (3*R*,3a*R*)-1,2,3,4,5,6-Hexahydro-3-methyl-3a*H*-indene-3a-carbaldehyde (11). Compounds **9**, **10**, and **11** were prepared from compound **B**[5] as follows: (i) a two-step sequence for **9** [(1) $LiAlH_4$, THF; (2) PCC, CH_2Cl_2]: (ii) a three-step sequence for **10** [(1) H_2/Pd–C, EtOH; (2) $LiAlH_4$, THF; (3) Swern oxidation]: (iii) a four-step sequence for **11** [(1) $HSCH_2CH_2$-

SH, $BF_3 \cdot OEt_2$; (2) Raney-Ni (W-2), EtOH; (3) $LiAlH_4$; (4) Swern oxidation].

9: A colorless oil; IR ($CHCl_3$) 2830, 2740, 1715, and 1660 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=1.15 (3H, d, J=7.9 Hz), 1.59—1.79 (2H, m), 1.89—2.18 (2H, m), 2.30 (1H, ddd, J=17.8, 13.5, 5.0 Hz), 2.41 (1H, ddd, J=17.8, 5.6, 2.3 Hz), 2.59—2.68 (1H, m), 2.70—2.78 (1H, m), 2.89 (1H, dddd, J=20.1, 10.6, 2.3, 2.3 Hz), 6.01 (1H, dd, J=2.3, 1.3 Hz), and 9.73 (1H, s); EIMS m/z (rel intensity) 178 (M^+, 77) and 149 (100). HREIMS. Found: m/z 178.0990. Calcd for $C_{11}H_{14}O_2$: M, 178.0994.

10: A colorless oil; IR ($CHCl_3$) 2820, 2720, and 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=1.06 (3H, d, J=7.4 Hz), 1.26—1.48 (2H, m), 1.72—1.83 (1H, m), 1.88—2.41 (7H, m), 2.48 (1H, dd, J=15.5, 5.9 Hz), 2.78—2.89 (1H, m), and 9.68 (1H, s); EIMS m/z (rel intensity) 180 (M^+, 100), 165 (7), 151 (35), and 133 (72). HREIMS. Found: m/z 180.1130. Calcd for $C_{11}H_{16}O_2$: M, 180.1150.

11: A colorless oil; IR ($CHCl_3$) 2830, 2720, and 1710 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=0.92—1.11 (1H, m), 1.06 (3H, d, J=7.3 Hz), 1.26—1.58 (2H, m), 1.68—1.83 (2H, m), 1.89—2.07 (3H, m), 2.25—2.48 (1H, m) , 2.48 (1H, ddd, J=12.9, 3.4, 3.4 Hz), 2.56—2.71 (1H, m), 5.61—5.66 (1H, m), and 9.63 (1H, s); EIMS m/z (rel intensity) 164 (M^+, 14), 149 (1), and 135 (100). HREIMS. Found: m/z 164.1207. Calcd for $C_{11}H_{16}O$: M, 164.1201.

Autoxidation of 9. Autoxidation of **9** (51.1 mg, 0.287 mmol) at 65 °C for 23 h and subsequent treatment with Ph_3P were performed as described above. The crude product was purified by column chromatography on silica gel [16 g, hexane–EtOAc (2 : 1→1 : 1→1 : 2)] to give a mixture of **12** and **13**. Further separation of this mixture by preparative TLC [hexane–EtOAc (1 : 3)] provided pure **12** (7.9 mg, 17%) and **13** (9.5 mg, 20%) as a colorless oil, respectively.

12 (the less polar compound): IR ($CHCl_3$) 3600, 3430, 1660, and 930 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=1.08 (3H, d, J=6.3 Hz), 1.61—1.78 (2H, m), 1.76 (1H, br s, -OH), 1.82—1.96 (2H, m), 2.22 (1H, ddd, J=13.9, 5.3, 2.0 Hz), 2.34—2.54 (2H, m), 2.67—2.82 (2H, m), and 5.85 (1H, dd, J=2.0, 1.0 Hz); EIMS m/z (rel intensity) 166 (M^+, 100), 148 (2), 138 (79), 124 (81), and 96 (87). HREIMS. Found: m/z 166.0996. Calcd for $C_{10}H_{14}O_2$: M, 166.0994.

13 (the more polar compound): IR ($CHCl_3$) 3600, 3420, 1660, and 935 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=0.87 (3H, d, J=7.3 Hz), 1.49 (1H, dddd, J=12.5, 8.2, 3.0, 1.3 Hz), 1.95 (1H, br s, -OH), 1.97—2.15 (2H, m), 2.17—2.45 (3H, m), 2.55 (1H, dddd, J=19.5, 8.2, 8.2, 2.0 Hz), 2.71 (1H, dddd, J=19.5, 9.5, 3.0, 1.0 Hz), 2.78 (1H, ddd, J=17.5, 12.2, 6.3 Hz), and 5.91 (1H, dd, J=2.0, 1.0 Hz); EIMS m/z (rel intensity) 166 (M^+, 48), 148 (3), 138 (100), 124 (98), and 96 (98). HREIMS. Found: m/z 166.1004. Calcd for $C_{10}H_{14}O_2$: M, 166.0994.

Autoxidation of 10. Autoxidation of **10** (58.5 mg, 0.325 mmol) at 65 °C for 23 h and subsequent treatment with Ph_3P were performed as described above. Treatment of the crude product with excess CH_2N_2 and subsequent separation by column chromatography on silica gel [18 g, hexane–EtOAc (5 : 1→5 : 2→1 : 1)] gave **14** (17.4 mg, 25%) as a colorless oil, along with the recovered **10** (7.2 mg, 12%).

14: IR ($CHCl_3$) 1715, 1225, and 1195 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=0.91 (3H, d, J=6.9 Hz), 1.22—1.50 (2H, m), 1.76—2.08 (4H, m), 2.13—2.63 (5H, m), 2.92—3.05 (1H, m), and 3.74 (3H, s); EIMS m/z (rel intensity) 210 (M^+, 42), 178 (100), and 150 (96). HREIMS. Found: m/z 210.1228. Calcd for $C_{12}H_{18}O_3$: M, 210.1256.

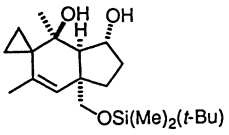
Autoxidation of 11. Autoxidation of **11** (88.4 mg, 0.539 mmol) at 65 °C for 23 h and subsequent treatment with Ph_3P were performed as described above. The crude product was subjected to separation by column chromatography on silica gel [30 g, hexane–ether (2 : 1→1 : 1→0 : 1)] to give a mixture of **15** and **16**, crude **17**, and crude **18**. Further purification by preparative TLC [$CHCl_3$–acetone (20 : 1) for the mixture of **15** and **16**; benzene–acetone (5 : 1) for **17**; benzene–acetone (7 : 1) for **18**] provided **15** (4.3 mg, 5%; a 1 : 1 mixture of diastereomers), **16** (4.1 mg, 5%), **17** (3.9 mg, 4%; a 1 : 1 : 2 : 2 mixture of diastereomers), and **18** (4.0 mg, 4%; a 1 : 1 mixture of diastereomers) as a colorless oil, respectively.

15: IR ($CHCl_3$) 3600, and 3450 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=0.98 (1.5H, d, J=6.9 Hz), 1.00 (1.5H, d, J=6.6 Hz), 1.20—1.43 (2H, m), 1.57—2.32 (8H, m), 2.35—2.62 (2H, m), and 4.12—4.21 (1H, m); EIMS m/z (rel intensity) 152 (M^+, 100), 137 (18), and 134 (16). HREIMS. Found: m/z 152.1229. Calcd for $C_{10}H_{16}O$: M, 152.1201.

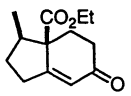
16: IR ($CHCl_3$) 1655 and 1630 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=1.11 (3H, d, J=7.3 Hz), 1.37—1.51 (1H, m), 1.98—2.62 (9H, m), and 2.76—2.92 (1H, m); EIMS m/z (rel intensity) 150 (M^+, 81), 135 (19), and 122 (100). HREIMS. Found: m/z 150.1047. Calcd for $C_{10}H_{14}O$: M, 150.1044.

17: IR ($CHCl_3$) 3600, and 3450 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=0.91—2.57 (15H, m), and 3.93—4.28 (1H, m); EIMS m/z (rel intensity) 168 (M^+, 13), 153 (16), 150 (11), and 111 (100). HREIMS. Found: m/z 168.1154. Calcd for $C_{10}H_{16}O_2$: M, 168.1150.

18: IR ($CHCl_3$) 3600, 3460, and 1715 cm^{-1}; ^1H NMR ($CDCl_3$, 270 MHz) δ=0.91—1.36 (2H, m), 1.18 (3H, d, J=7.3 Hz), 1.51—2.52 (10H, m), and 2.66—2.75 (1H, m); EIMS m/z (rel intensity) 168 (M^+, 43), 153 (5), 150 (13), 126 (100), and 84 (91). HREIMS. Found: m/z 168.1125. Calcd for $C_{10}H_{16}O_2$: M, 168.1150.



A



B

References

1) H. Kigoshi, A. Sawada, Y. Nakayama, H. Niwa, and K. Yamada, *Tetrahedron Lett.*, **30**, 1983 (1989).

2) H. Kigoshi, Y. Imamura, H. Niwa, and K. Yamada, *J. Am. Chem. Soc.*, **111**, 2302 (1989).

3) F. A. Carey and R. J. Sundberg, "Advanced Organic Chemistry, Part A," Plenum, New York (1990), Chap. 12.

4) H. Kigoshi, A. Sawada, Y. Imamura, H. Niwa, and K. Yamada, *Tetrahedron*, **45**, 2551 (1989).

5) P. R. Vettel and R. M. Coates, *J. Org. Chem.*, **45**, 5430 (1980).