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Regioselective Transformation of the Functional Groups of Coenzyme PQQ

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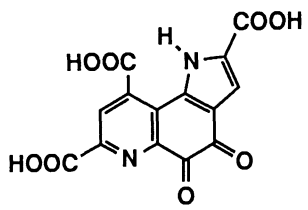
Regioselective transformation of the carboxyl groups of PQQ was performed by applying the regioselective hydrolysis of the three methyl ester groups of trimethyl 5-methoxy-1*H*-pyrrolo[2,3-f]quinoline-2,7,9-tricarboxylate (**1**).

PQQ (4,5-dihydro-4,5-dioxo-1*H*-pyrrolo[2,3-f]quinoline-2,7,9-tricarboxylic acid) has been shown to be a prosthetic group of several important oxidoreductases not only from prokaryotes but also from eukaryotes, and its chemical and biological functions have recently been noted in various fields of research.[1] In order to study and apply such functions, chemical modification of PQQ must be an important strategy.



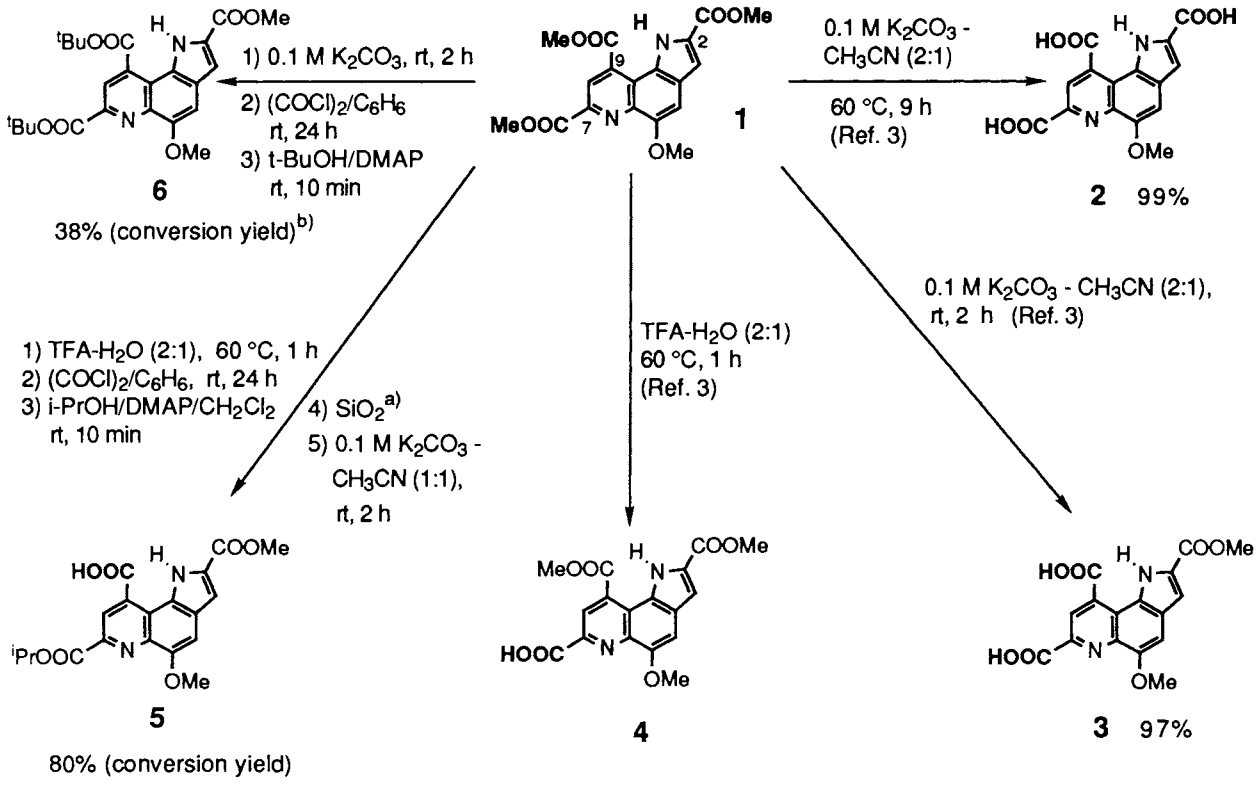
Coenzyme PQQ

Thus in this paper, we would like to demonstrate the regioselective transformations of the carboxyl groups of coenzyme PQQ. We have already reported the regioselective hydrolysis of the three methyl ester groups of **1** [2] by utilizing subtle diference of their susceptibilities to hydrolysis to give the carboxylic acid derivatives **2**, **3**, and **4**, respectively.[3] This method was further developed to approach the present purpose.

The selective hydrolysis of the methyl ester group at the 9-position of **1** was accomplished as shown in Fig. 1. After protection of the carboxyl group of **4** as the *iso*-propyl ester, the 9-methyl ester group was hydrolyzed in 0.1 M K_2CO_3 - CH_3CN (1:1) at room temperature for 2 h to give **5**.[4] In order to synthesize a 2-monocarboxylic acid derivative by the similar methodology, **6** [5] was first prepared from **3** since *t*-butyl ester is much robuster toward alkaline hydrolysis than methyl ester. Hydrolysis of **6** under several alkaline conditions, however, was found to give 7-monocarboxylic acid derivative as a major product instead of the desired 2-monocarboxylic acid derivative.

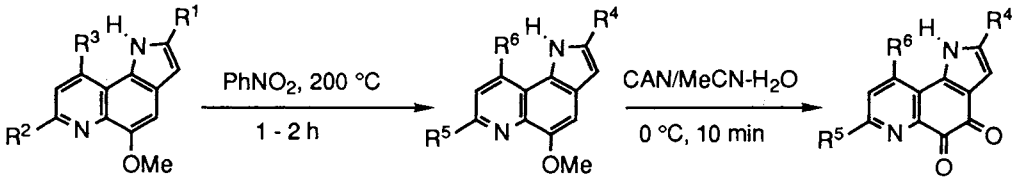
Decarboxylation of the carboxyl groups of **3** and **4** has been already demonstrated to give **8** and **9** which were successfully applied to the syntheses of 7,9-didecarboxy PQQ (**12**) and 7-decarboxy PQQ (**13**), respectively.[3] Decarboxylation of **5** also proceeded under the same conditions (in nitrobenzene at 200 °C for 1-2 h) to give **10** which was then converted into the

corresponding quinone **14** by the oxidation with CAN (cerium (IV) ammonium nitrate).[6] The tridecarboxy derivative **7** can be also obtained by decarboxylation of **2**, but the oxidation of **7** to the corresponding quinone **11** has not been succeeded yet because of its instability under the strongly acidic conditions of the oxidation reaction.[3]



a) Flash Chromatography, 52 % of **1** was recovered.
b) 47 % of **3** was obtained.

Fig. 1.



(1)

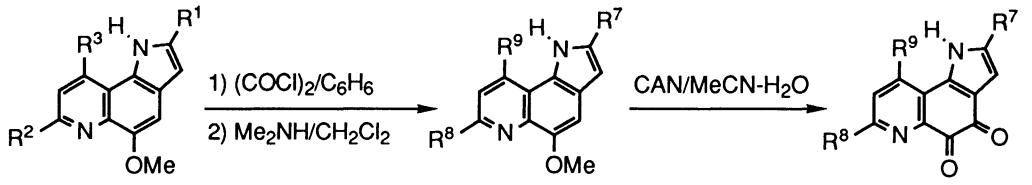
2: $R^1=R^2=R^3=COOH$
3: $R^1=COOMe$, $R^2=R^3=COOH$
4: $R^1=R^3=COOMe$, $R^2=COOH$
5: $R^1=COOMe$, $R^2=COO^iPr$, $R^3=COOH$

7: $R^4=R^5=R^6=H$, 56 %
8: $R^4=COOMe$, $R^5=R^6=H$, 94 %
9: $R^4=R^6=COOMe$, $R^5=H$, 64 %
10: $R^4=COOMe$, $R^5=COO^iPr$, $R^6=H$, 73 %

11: 0 %
12: 71 %
13: 56 %
14: 39 %

Transformation of the carboxyl groups of **2** - **5** to chloroformyl group was then examined, since it can be converted into a wide variety of functional groups. In the present study, an amidation reaction is demonstrated, because amide derivatives of PQQ are considered to be very important model compounds[7] in connection with the binding mode of PQQ into the active sites of quinoprotein amine oxidases.[1]

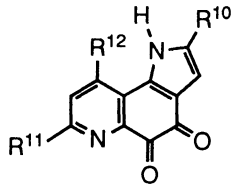
Treatment of **2** (100 mg, 0.303 mmol) with oxalyl chloride (9.09 mmol) in dry benzene (2 ml) at room temperature for 10 h followed by evaporation of the remaining oxalyl chloride and the solvent gave the corresponding carbonyl chloride derivative as a red solid, which was then converted into the tris(dimethylcarbamoyl) derivative **15** by the reaction with dimethylamine in CH_2Cl_2 (94% yield). The carboxyl groups of **3**, **4**, and **5** were also transformed chemoselectively to the dimethylcarbamoyl groups to give **16**, **17** and **18** by the same treatment, respectively. These dimethylcarbamoyl derivatives **15** - **18** were easily oxidized to the corresponding quinones **19** - **22** by the usual method using CAN.[8]



(2)

2	**15**: R^7=R^8=R^9=$CONMe_2$, 94 %	**19**: 65 %
3	**16**: R^7=COOMe, R^8=R^9=$CONMe_2$, 68 %	**20**: 68 %
4	**17**: R^7=R^9=COOMe, R^8=$CONMe_2$, 55 %	**21**: 58 %
5	**18**: R^7=COOMe, R^8=COO^iPr, R^9=$CONMe_2$, 97 %	**22**: 47 %

The present methodology was applicable to the synthesis of PQQ model compounds which have amino acid residues such as -NH-Ala-OMe and -NH-Leu-OMe (**23** and **24**) and a long chain alkyl group (**25** - **28**). We are now examining catalytic activities of the model compounds in the aerobic autorecycling oxidation of several substrates such as amines, amino acids, thiols, glucose, and so on.



23: R^{10}=R^{11}=R^{12}=$CONHCH(CH_3)COOMe$
24: R^{10}=R^{11}=R^{12}=$CONHCH(COOMe)CH_2CHMe_2$
25: R^{10}=R^{11}=R^{12}=$CONHC_{12}H_{25}$
26: R^{10}=COOMe, R^{11}=R^{12}=$CONHC_{12}H_{25}$
27: R^{10}=R^{12}=COOMe, R^{11}=$CONHC_{12}H_{25}$
28: R^{10}=COOMe, R^{11}=COO^iPr, R^{12}=$CONHC_{12}H_{25}$

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References

1) J. A. Duine, J. Frank, and J. A. Jongejan, *Adv. Enzymol.*, **59**, 170 (1987); C. Hartmann and J. P. Klinman, *BioFactors*, **1**, 41 (1988), and references cited therein.

2) Compound **1** is a key intermediate of the PQQ-synthesis by the Corey's method; E. J. Corey and A. Tramontano, *J. Am. Chem. Soc.*, **103**, 5599 (1981).

3) S. Itoh, J. Kato, T. Inoue, Y. Kitamura, M. Komatsu, and Y. Ohshiro, *Synthesis*, **1987**, 1067.

4) **5**: mp > 300 °C; ^{1}H-NMR (d_4-methanol) δ = 1.49 (d, J = 6.3 Hz, 6H, -CH($\underline{CH_3}$)$_2$), 3,97 (s, 3H, -OCH_3), 4.10 (s, 3H, -OCH_3), 5.43 (sep, J = 6.3 Hz, 1H, -C$\underline{H}$(CH_3)$_2$), 7.49 (br s, 1H, 3-H), 7.64 (s, 1H, 4-H), 8.87 (s, 1H, 8-H); IR (KBr) 3500 - 3600 (OH), 3472 (NH), 1718 (C=O, ester), 1695 cm^{-1} (C=O, carboxyl).

5) **6**: mp (dec) = 124 - 126 °C; ^{1}H-NMR ($CDCl_3$) δ = 1.69 (s, 9H, -C($\underline{CH_3}$)$_3$), 1.76 (s, 9H, -C($\underline{CH_3}$)$_3$), 3.98 (s, 3H, -OCH_3), 4.10 (s, 3H, -OCH_3), 7.26 (s, 1H, 4-H), 7.30 (d, J = 1.7 Hz, 1H, 3-H), 8.73 (s, 1H, 8-H), 11.90 (br s, 1H, NH); IR (KBr) 3464 (NH), 1720 cm^{-1} (C=O, ester); MS m/z = 456 (M$^+$).

6) **14**: mp (dec) > 300 °C; ^{1}H-NMR ($CDCl_3$) δ = 1.49 (d, J = 6.4 Hz, 6H, -CH($\underline{CH_3}$)$_2$), 4.00 (s, 3H, -$COOCH_3$), 5.33 (sep. J = 6.4 Hz, 1H, -C$\underline{H}$(CH_3)$_2$), 7.34 (d, J = 2.3 Hz, 1H, 3-H), 8.37 (d, J = 8.9 Hz, 1H, 9-H), 8.95 (d, J = 8.9 Hz, 1H, 8-H), 13.60 (br s, 1H, NH); IR (KBr) 3455 (NH), 1716 (C=O, ester), 1686 cm^{-1} (C=O, quinone); MS m/z = 344 (M$^+$+2, characteristic peak for *o*-quinones), 342 (M$^+$).

7) M. Mure, K. Nii, T. Inoue, S. Itoh, and Y. Ohshiro, *J. Chem. Soc., Perkin Trans. 2*, **1990**, 315.

8) **19**: mp (dec) 185 -187 °C; ^{1}H-NMR ($CDCl_3$) δ = 3.01 (s, 3H, -NCH_3), 3.15 (s, 3H, -NCH_3), 3.24 (s, 6H, -N(CH_3)$_2$), 3.32 (s, 6H, -N(CH_3)$_2$), 7.10 (d, J = 1.7 Hz, 1H, 3-H), 7.84 (s, 1H, 8-H), 10.91 (br s, 1H, NH); IR (KBr) 3444 (NH), 1686 (C=O, quinone), 1638 cm^{-1} (C=O, amide); MS m/z = 413 (M$^+$+2, characteristic peak for *o*-quinones), 411 (M$^+$). **20**: mp (dec) 172 -173 °C; ^{1}H-NMR ($CDCl_3$) δ = 3.06 (s, 3H, -NCH_3), 3.16 (s, 3H, -NCH_3), 3.27 (s, 3H, -NCH_3), 3.32 (s, 3H, -NCH_3), 3.94 (s, 3H, -OCH_3), 7.34 (d, J = 2.9 Hz, 1H, 3-H), 7.86 (s, 1H, 8-H), 10.17 (br s, 1H, NH); IR (KBr) 3456 (NH), 1722 (C=O, ester), 1684 (C=O, quinone), 1634 cm^{-1} (C=O, amide); MS m/z = 400 (M$^+$+2, characteristic peak for *o*-quinones), 398 (M$^+$). **21**: mp (dec) 239 -241 °C; ^{1}H-NMR ($CDCl_3$) δ = 3.03 (s, 3H, -NCH_3), 3.34 (s, 3H, -NCH_3), 3.96 (s, 3H, -OCH_3), 4.04 (s, 3H, -OCH_3), 7.41 (d, J = 2.7 Hz, 1H, 3-H), 8.16 (s, 1H, 8-H), 11.09 (br s, 1H, NH); IR (KBr) 3432 (NH), 1726 (C=O, ester), 1686 (C=O, quinone), 1632 cm^{-1} (C=O, amide); MS m/z = 387 (M$^+$+2, characteristic peak for *o*-quinones), 385 (M$^+$). **22**: mp (dec) 189 - 192 °C; ^{1}H-NMR ($CDCl_3$) δ = 1.44 (d, J = 6.5 Hz, 6H, -CH($\underline{CH_3}$)$_2$), 3.04 (s, 3H, -NCH_3), 3.45 (s, 3H, -NCH_3), 3.94 (s, 3H, -OCH_3), 5.33 (sep. J = 6.5 Hz, 1H, -C$\underline{H}$(CH_3)$_2$), 7.28 (d, J = 1.5 Hz, 1H, 3-H), 8.10 (s, 1H, 8-H), 11.03 (br s, 1H, NH); IR (KBr) 3468 (NH), 1722 (C=O, ester), 1690 (C=O, quinone), 1630 cm^{-1} (C=O, amide); *MS* m/z = 416 (M$^+$+2, characteristic peak for *o*-quinones), 414 (M$^+$).

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