TRANSFORMATION OF ASTERRIQUINONE DIACETATE TO ASTERRIQUINONE MONOALKYL ETHER VIA ITS MONOACETAL

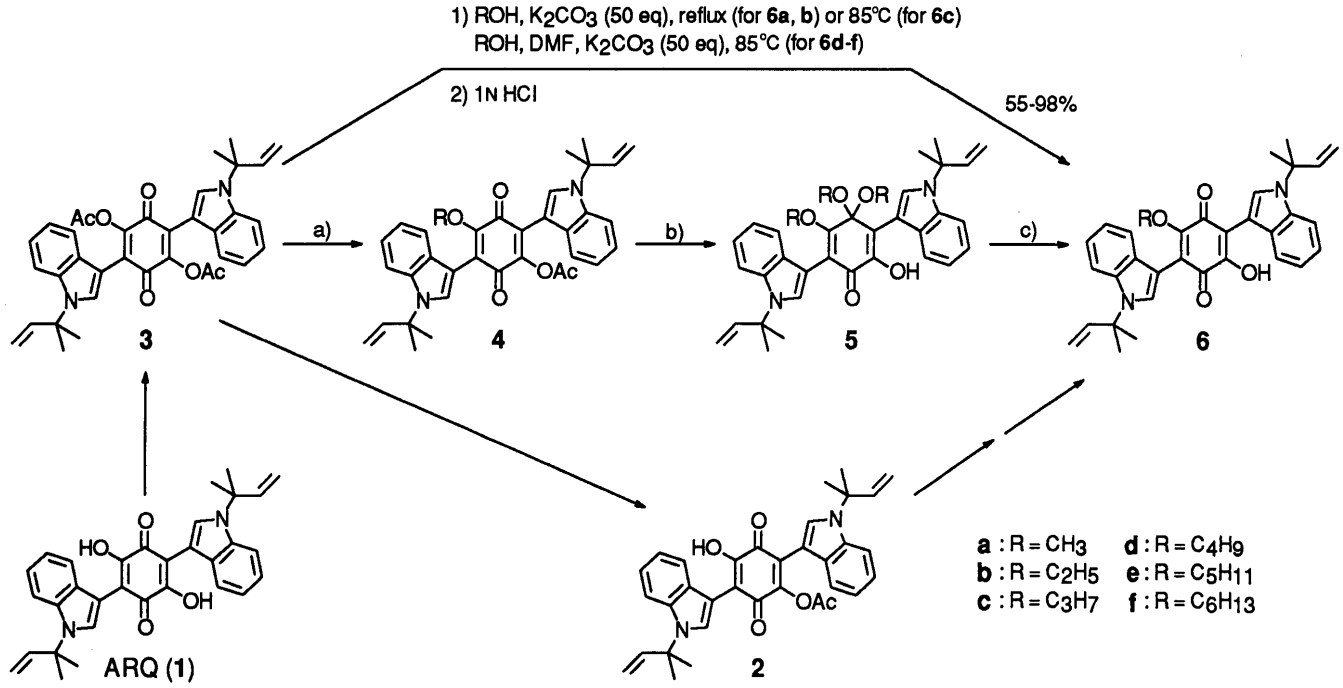
Akira KAJI,* Ryo SAITO, Yukako SHINBO, and Noriki KIRIYAMA
Faculty of Pharmaceutical Sciences, Hokuriku University, Ho-3, Kanagawa-machi, Kanazawa 920-11, Japan

Asterriquinone (ARQ) diacetate; 2,5-bis[1-(1,1-dimethyl-2-propenyl)-1*H*-indol-3-yl]-3,6-diacetoxy-2,5-cyclohexadiene-1,4-dione (**3**), was converted into ARQ monoalkyl ether (**6**) by treatment with a mixture of alcohol and K_2CO_3 under heating, followed by acidification. The reaction was shown to proceed via ARQ monoacetate monoalkyl ether (**4**) and ARQ monoacetal monoalkyl ether (**5**).

KEY WORDS asterriquinone monoalkyl ether; asterriquinone diacetate; asterriquinone; asterriquinone monoacetal monoalkyl ether; *Aspergillus terreus* IFO 6123

An antitumor agent, Asterriquinone (ARQ); 2,5-bis[1-(1,1-dimethyl-2-propenyl)-1*H*-indol-3-yl]-3,6-dihydroxy-2,5-cyclohexadiene-1,4-dione (**1**) and its monoacetate (**2**) are metabolites of *Aspergillus terreus* IFO 6123.[1] ARQ monomethyl ether (**6a**)[2] derived from **2** inhibited cell growth of mouse leukemia P388 cells with a potency similar to ARQ (**1**). We previously reported that ARQ diacetate (**3**) derived from ARQ (**1**) was converted into **2** by treatment with 5% aq. $NaHCO_3$ in pyridine, and **6a** was prepared from **2** via 2-step reactions.[2] The present investigation was undertaken to discover a superior method for the preparation of various monoalkyl ethers (**6**) from **3**.

In this paper, we report that **6** was directly obtained from **3** in good yield. Thus, **3** was treated with a mixture of MeOH and K_2CO_3 under reflux for 10 min. The reaction mixture was filtered, the filtrate was poured into 1 N HCl, and the resulting precipitate was purified by column chromatography on SiO_2 to give



a) ROH, $NaHCO_3$ (1 eq), reflux (for **4a, b**) or 85°C (for **4c**); b) MeOH, K_2CO_3 (1 eq), reflux (for **5a**). ROH, K_2CO_3 (20 eq), reflux (for **5b**) or 85°C (for **5c**); c) MeOH, 1 N HCl.

Chart 1

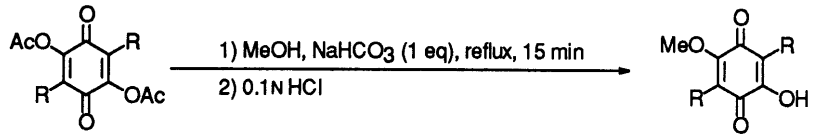
* To whom correspondence should be addressed.

6a (yield, 98%). Similarly, with other alcohols (from ethanol to hexanol), the corresponding monoalkyl ethers (**6b-f**) were obtained (yield, 55-93%).

As the transformation of quinone diacetate to quinone monoalkyl ether has not been previously reported, more detailed study of this reaction was carried out. Compound **3** was treated with a mixture of MeOH and $NaHCO_3$ under reflux for 1 h to give ARQ monoacetate monomethyl ether (**4a**, yield, 98%).[2] Compound **4a** was treated with a mixture of MeOH and K_2CO_3 under reflux for 10 min to give the monodimethyl acetal of **6a** (**5a**, yield, 90%).[3] Compound **5a** was hydrolyzed by a mixture of MeOH and 1 N HCl to give **6a** quantitatively. The position of the acetal group in **5a** was determined by the results obtained from difference NOE experiments.

From the above results, it was shown that **3** was converted into **6** via **4** and **5**. As examples of the preparation of quinone acetals, anodic oxidation of 1,4-dialkoxyaromatic compounds and chemical oxidation of phenols have been known.[4] But, no direct acetal formation from quinone by alcohol and alkali has been reported before. Similarly, diethyl- and dipropyl acetal (**5b** and **5c**, yield, 86% and 75% from **3**, respectively) were also obtained (Chart 1).

In addition, 2,5-diacetoxy-*p*-benzoquinone (**7a**)[2] and 2,5-diacetoxy-*p*-xyloquinone (**7b**)[2] were also converted into 2-hydroxy-5-methoxy-*p*-benzoquinone (**8a**)[2] and 2-hydroxy-5-methoxy-*p*-xyloquinone (**8b**)[2] in good yield, respectively (Chart 2).



7a : R = H
7b : R = CH_3

8a : 88%[5]
8b : 92%

Chart 2

In conclusion, this convenient method for the synthesis of quinone monoalkyl ether would be applicable to other polyhydroxyquinone derivatives.

ACKNOWLEDGMENT We are grateful to the Institute for Fermentation, Osaka, for supplying *Aspergillus terreus* IFO 6123. We would like to thank Professor H. Sawanishi of our university for helpful advice. Thanks are also due to Mrs. K. Shiratori and Miss C. Takano of our university for elemental analysis and MS measurement. This work was supported in part by the Special Research Fund of Hokuriku University.

REFERENCES AND NOTES

1) a) Yamamoto Y., Nishimura K., Kiriyama N., *Chem. Pharm. Bull.*, **24**, 1853-1859 (1976); b) Kaji A., Iwata T., Kiriyama N., Wakusawa S., Miyamoto K., *Chem. Pharm. Bull.*, **42**, 1682-1684 (1994).

2) Kaji A., Kimura K., Iwata T., Kiriyama N., *Chem. Pharm. Bull.*, **43**, 1818-1820 (1995).

3) Data for **5a**: bright yellow prisms from *n*-hexane, mp 165-166°C (dec.). *Anal.* calcd for $C_{35}H_{38}N_2O_5$: C, 74.18; H, 6.76; N, 4.94. Found: C, 74.17; H, 6.82; N, 4.87. IR (KBr) cm^{-1}: 3248, 1638, 1322, 1062. ^1H-NMR ($CDCl_3$) δ: 1.82 (6H, s, $C(C\underline{H}_3)_2CH=CH_2$), 1.83 (6H, s, $C(C\underline{H}_3)_2CH=CH_2$), 3.33 (6H, s, $2OCH_3$), 3.59 (3H, s, OCH_3), 5.21 (1H, d, *J*=17.6 Hz, $C(CH_3)_2CH=C\underline{H}_2$), 5.264 (1H, d, *J*=10.6 Hz, $C(CH_3)_2CH=C\underline{H}_2$), 5.267 (1H, d, *J*=17.6 Hz, $C(CH_3)_2CH=C\underline{H}_2$), 5.272 (1H, d, *J*=10.6 Hz, $C(CH_3)_2CH=C\underline{H}_2$), 6.20 (1H, dd, *J*=10.6, 17.6 Hz, $C(CH_3)_2C\underline{H}=CH_2$), 6.23 (1H, dd, *J*=10.6, 17.6 Hz, $C(CH_3)_2C\underline{H}=CH_2$), 6.36 (1H, s, OH), 7.12-7.19 (4H, m, Ar-H), 7.49-7.51 (1H, m, Ar-H), 7.57-7.60 (2H, m, Ar-H), 7.66 (1H, s, Ar-H), 7.83-7.85 (1H, m, Ar-H), 7.93 (1H, s, Ar-H).

4) Swenton J. S., " The Chemistry of the Quinonoid Compounds, " Vol. 2, Part 2, ed. by Patai S. and Rappoport Z., John Wiley and Sons, Inc., New York, 1988, p. 899.

5) Compounds **8a** and **8b** were purified by column chromatography on oxalic acid-impregnated SiO_2.

(Received October 21, 1996; accepted November 14, 1996)