REGIOSELECTIVE SYNTHESIS OF NAPHTHACENEQUINONES USING SULFOLENE

Seiichi Takano*, Susumi Hatakeyama, Kunio Ogasawara, and Tetsuji Kametani
Pharmaceutical Institute, Tohoku University, Aobayama, Sendai 980, Japan

Abstract—Starting with naphthazarin diacetate(2) and sulfolene(3), naphthacenequinones, (14) and (15), have been synthesized regioselectively.

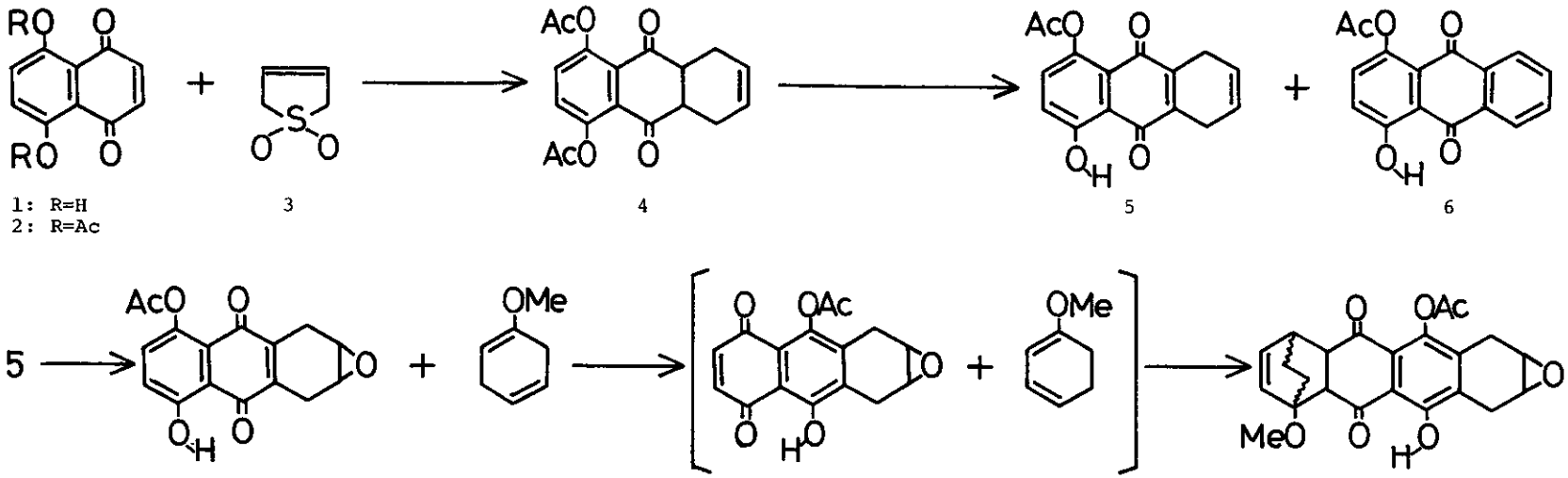
In connection with studies toward the synthesis of the antitumor anthracyclines[1], a regiochemically controlled cycloaddition based on the finding of Inhoffen and Muxfeldt[2] has been extensively studied by several groups.[3~6] Present report describes an application of these results which allows a regioselective formation of naphthacenequinones, 14 and 15, starting with naphthazarin diacetate(2) and sulfolene(3).

Naphthazarin diacetate(2), prepared in 87 % yield from naphthazarin[7](1), was heated at 125~130 °C with an equimolar amount of sulfolene(3) in a sealed tube in the presence of hydroquinone to give a tricyclic adduct(4) in 80 % yield.[8] Treatment of 4 with bubbling oxygen in a mixture of 1 % KOH solution and tetrahydrofuran(1:2)[4b,c] at room temperature allowed a concomitant oxidation and specific hydrolysis to give a 50 % yield of the naphthoquinone monoacetate(5) accompanied by a 4.6 % yield of the anthraquinone derivative(6). To our knowledge such a specific monodeacylation under the oxidative conditions is unprecedented and is particularly noteworthy. Oxidation of 5 with m-chloroperbenzoic acid in methylene chloride[4c] at room temperature for 3 days afforded the corresponding epoxide(7) in 87 % yield, which on treatment with an excess of 1-methoxycyclohexa-1,4-diene(8) in chloroform at room temperature for 7 days furnished the adduct(11) in a regiochemically pure form in 55 % yield(66 % yield based on consumed 7) apparently through the intermediacy of 9 and 10. Reported papers[3,4a,b,c,e] described use of 1-methoxycyclohexa-1,3-diene(10) in the related reaction, however the present investigation revealed utility of the more readily available 1,4-diene(8) when the reaction is carried out in a chloroform solution. As the reaction could not be initiated in other solvents, chloroform itself or its

contaminants could have some special effects on the isomerization of the 1,4-diene(8) to the 1,3-diene.[9]

Oxidation of the adduct(11) to the corresponding benzoquinone(12) was extremely difficult owing to concurrent aromatization of the ring bearing epoxide. Oxidation of 12 with active lead dioxide[4c] in chloroform at 55 °C for 6 days gave 12 in only 5 % yield accompanied by the aromatic compound(13) in 56 % yield. Some improvement could be achieved by employing Saegusa's condition,[10] however the yield of 12 was 20 % at best. Thus, treatment of 11 with lithium diisopropylamide in tetrahydrofuran at -78 °C, followed by cupric chloride in dimethylformamide afforded a 20 % yield of 12 and a 37 % yield of 13. On the other hand, oxidation of 11 with silver oxide recovered the starting material, and oxidation with DDQ in boiling benzene regenerated 7 by retro-Diels-Alder reaction presumably through 9. Attempts to cleave the epoxide ring using boron trifluolide, magnesium bromide,[11] or ethyl iodide in the presence of sodium iodide,[12] prior to the oxidation, were unsuccessful owing to formation of a complex mixture in each reaction.

Pyrolysis[4b,c] of 12 and 13 at 160 °C under reduced pressure allowed a quantitative formation of 14 and 15, respectively. Since no regioisomer could be detected in each reaction, the regiochemical homogeneity of the adduct 11 was established rigorously Present investigation could not show unambiguous evidences to eliminate an alternative structure for each acetate, however the structures could be fully predictable by reported results, especially by Kelly's investigations.[4] Further structure confirmation and regioselective cleavage of the epoxide ring of 12 are now under investigation.

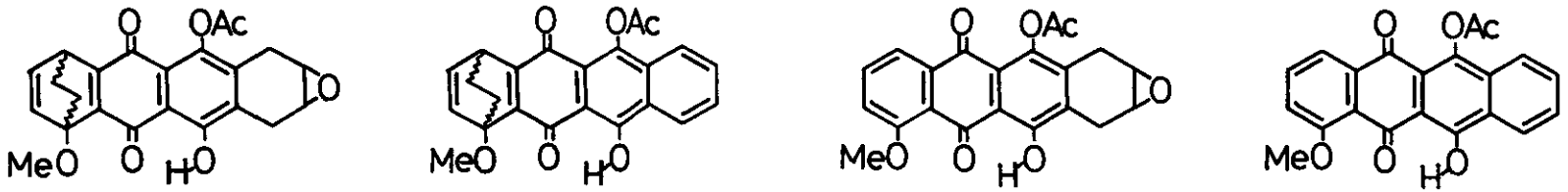


1: R=H
2: R=Ac

3 4 5 6

7 8 9 10 11

Scheme 1



12 13 14 15

Scheme 2

Experimental

Melting points were determined on a Yanagimoto MP-S2 apparatus and are uncorrected. IR spectra were measured with a Shimadzu IR 400 spectrometer, NMR spectra with a JEOL PMX 60 spectrometer(tetramethylsilane as an internal reference in deuteriochloroform solution), and mass spectra with Hitachi M-53 spectrometer.

Naphthazarin Diacetate(2)

A mixture of naphthazarin(1)(1.90 g, 10 mmol) and acetic anhydride(9.4 ml, 100mmol) in benzene(15 ml) was refluxed for 20 h. The reaction mixture was evaporated in vacuo to leave a tan crystalline mass, which on recrystallization from benzene gave naphthazarin diacetate(2)(2.35 g, 87.0 %) : mp 200∿201 °C; IR(Nujol) 1755, 1660 cm^{-1}; NMR δ 2.40(6H,s), 6.81(2H,s), 7.40(2H,s); MS m/e 274(M^+), 232, 190. Anal. Calcd. for $C_{14}H_{10}O_6$: C, 61.32; H, 3.68. Found : C,61.20; H, 3.63.

1,4-Diacetoxy-5,8,8a,10a-tetrahydroanthracene-9,10-dione(4)

A mixture of (2)(8.42 g, 30.7 mmol) and sulfolene(3)(3.78 g, 32.0 mmol) in benzene (50 ml) was heated at 125∿130 °C under argon in the presence of hydroquinone(40 mg) using a sealed tube. After 6 h, the reaction mixture was concentrated in vacuo to leave a brown crystalline residue(10.3g), which on recrystallization from benzene gave 1,4-diacetoxy-5,8,8a,10a-tetrahydroanthracene-9,10-dione(4)(8.10 g, 80.4 %) as pale yellow needles : mp 185∿186 °C; IR(Nujol) 1770, 1708, 1692 cm^{-1}; NMR δ 2.43 (6H,s), 3.35(2H,m), 5.78(2H, br.s), 7.42(2H,s); MS m/e 328(M^+), 244, 226. Anal. Calcd. for $C_{18}H_{16}O_6$: C, 65.85; H, 4.91. Found : C, 65.69; H, 4.95.

1-Acetoxy-5,8-dihydro-4-hydroxyanthracene-9,10-dione(5) and 1-Acetoxy-4-hydroxy-anthracene-9,10-dione(6)

Into a stirred solution of 4(6.56 g, 20 mmol) in a mixture of 1 % KOH(200 ml) and tetrahydrofuran(400ml) was bubbled oxygen at room temperature for 4 h. After acidified with 10 % HCl(pH 4∿5), the organic layer was separated and washed with brine. The aqueous layer was extracted thoroughly with methylene chloride, and the extract was washed with brine. The combined organic layer was dried over Na_2SO_4 and concentrated in vacuo to leave a dark brown crystalline residue(6.60 g), which was purified by column chromatography on silica gel(200 g). Elution with methylene

chloride gave 1-acetoxy-5,8-dihydro-4-hydroxyanthracene-9,10-dione(5)(2.85 g, 50.1 %) and 1-acetoxy-4-hydroxyanthracene-9,10-dione(6)(0.28 g, 4.6 %).

The quinone(5), after recrystallization from benzene, showed the following characteristics : orange needles; mp 189∿190 °C; IR(Nujol) 1760, 1660, 1640, 1620 cm^{-1}; NMR ($CDCl_3$+CF_3CO_2H) δ 2.53(3H,s), 3.25(4H,s), 5.95(2H,s), 7.38(2H,s); MS m/e 286, 285, 284(M^+), 283, 283, 282, 242, 224. Anal. Calcd. for $C_{16}H_{12}O_5$: C, 67.60; H,4.26. Found : C, 67.48; H, 4.08.

The quinone(6), after recrystallization from benzene, showed the following characteristics : light yellow needles; mp 184∿185 °C; IR(Nujol) 1760, 1672, 1630 cm^{-1}; NMR δ 2.44(3H,s), 7.35(2H,s), 7.80(2H,m), 8.25(2H,m), 13.29(1H,s, disappeared with D_2O); MS m/e 282(M^+), 240, 212, 184. Anal. Calcd. for $C_{16}H_{10}O_5$: C, 68.08; H, 3.57. Found : C, 68.64; 3.49.

1-Acetoxy-6,7-epoxy-5,6,7,8-tetrahydro-4-hydroxyanthracene-9,10-dione(7)

A mixture of 5(1.55 g, 5.4 mmol) and m-chloroperbenzoic acid(85 % purity, 2.60 g, 12.8 mmol) in methylene chloride(150 ml) was stirred at room temperature for 3 days. The precipitated m-chlorobenzoic acid was removed by filtration, and the filtrate was washed with 2 % $Na_2S_2O_4$, saturated $NaHCO_3$, and brine. The organic layer was dried over Na_2SO_4 and was concentrated in vacuo to leave an orange powder(1.63 g). Recrystallization from acetone gave 1-acetoxy-6,7-epoxy-5,6,7,8-tetrahydro-4-hydroxyanthracene-9,10-dione(7)(1.41 g, 87 %) as light yellow needles : mp 174∿175 °C; IR(Nujol) 1760, 1630 cm^{-1}; NMR δ 2.34(3H,s), 3.50(2H,m), 7.30(2H,s), 12.5(1H,s), disappeared with D_2O); MS m/e 300(M^+), 258, 240, 229, 212, 184. Anal. Calcd. for $C_{16}H_{12}O_6$: C, 64.00; H, 4.03. Found : C, 63.78; H, 4.01.

6-Acetoxy-8,9-epoxy-1,4-ethano-1,4,4a,7,8,9,10,12a-octahydro-11-hydroxy-1-methoxy-naphthacene-5,12-dione(11)

A mixture of 7(900 mg, 3 mmol) and 1-methoxycyclohexa-1,4-diene(6.0 ml) in chloroform (90 ml) was stirred under nitrogen at room temperature for a week. After evaporation of chloroform,a remaining volatile material was removed below 80 °C(0.1 Torr) using a Kugelrohr unit to give a dark brown residue which was crystallized from Et_2O to give 6-acetoxy-8,9-epoxy-1,4-ethano-1,4,4a,7,8,9,10,12a-octahydro-11-hydroxy-1-methoxynaphthacene-5,12-dione(11)(680 mg, 55.3 %) as pale yellow needles : mp 165∿166 °C; IR(Nujol) 1765, 1680, 1625 cm^{-1}; NMR δ 1.20∿2.20(5H,m), 2.38(3H,s), 3.49 (3H,s), 6.00(2H,m); MS m/e 300($M-C_7H_{10}O$), 258, 240, 229, 212, 184. Anal. Calcd.

for $C_{23}H_{22}O_7$: C, 67.31; H, 5.40. Found : C, 66.81; H, 5.40.

6-Acetoxy-8,9-epoxy-1,4-ethano-1,4,7,8,9,10-hexahydro-11-hydroxy-1-methoxynaphthacene-5,12-dione(12) and 6-Acetoxy-1,4-ethano-1,4-dihydro-11-hydroxy-1-methoxynaphthacene-5,12-dione(13)

(a) A suspension of 11(100 mg, 0.24 mmol) and PbO_2(700 mg, 2.4 mmol) in chloroform was heated under nitrogen at 55 °C for 6 days. The mixture was filtered through Celite, and the filtrate was concentrated in vacuo to leave a brown residue(110 mg). Preparative thin layer chromatography on silica gel developed with AcOEt-C_6H_6 (1:4) gave 6-acetoxy-8,9-epoxy-1,4-ethano-1,4,7,8,9,10-hexahydro-11-hydroxy-1-methoxynaphthacene-5,12-dione(12)(5 mg, 5.1 %) as a light brown amorphous powder : NMR δ 1.20∿2.10(4H,m), 2.50(3H,s), 3.76(3H,s), 4.18(1H, br.s), 6.33∿7.00(2H,m), 13.35(1H,s, disappeared with D_2O); MS m/e 380(M-C_2H_4), 338, 320, 310, 302, 191, and 6-acetoxy-1,4-ethano-1,4-dihydro-11-hydroxy-1-methoxynaphthacene-5,12-dione(13) (52 mg, 55.6 %) as light brown prisms(AcOEt-benzene) : mp 179∿180 °C; IR(Nujol) 1765, 1660, 1630 cm^{-1}; NMR δ 1.40∿2.10(4H,m), 2.56(3H,s), 3.83(3H,s), 4.26(1H, br.s), 6.40∿7.00(2H,m), 7.80(2H,m), 8.33(2H,m), 14.00(1H,s, disappeared with D_2O); MS m/e 360(M-C_2H_2), 320, 302.

(b) To a stirred solution of lithium diisopropylamide, prepared from diisopropylamine (0.1 ml, 0.7 mmol) and n-BuLi in n-hexane(10 (W/V)%, 0.45 ml, 0.7 mmol) in tetrahydrofuran(5.0 ml), under nitrogen at -78 °C was added 11(100 mg, 0.24 mmol). After stirring for 15 min at the same tempereture, a solution of anhydrous $CuCl_2$(67 mg, 0.5 mmol) in anhydrous dimethylformamide(1.0 ml) was added, and the resulting dark green solution was stirred for 2 h at -78 °C and the mixture was stirred for 2 days at room temperature. The reaction mixture was acidified with 3 % HCl and extracted with chloroform. The extract was washed twice with 3 % HCl and brine, and dried over Na_2SO_4. Removal of the solution in vacuo left a dark brown crystalline residue (120 mg), which on preparative thin layer chromatography on silica gel developed with AcOEt-C_6H_6(1:4) gave 12(20 mg, 20.4 %) and 13(35 mg, 37.4 %).

6-Acetoxy-8,9-epoxy-7,8,9,10-tetrahydro-11-hydroxy-1-methoxynaphthacene-5,12-dione(14)

The compound 12(10 mg, 0.024 mmol) was heated under reduced pressure(15 Torr) at 160 °C for 20 min to give 6-acetoxy-8,9-epoxy-7,8,9,10-tetrahydro-11-hydroxy-1-methoxynaphthacene-5,12-dione(14)(8 mg, 88.7 %) as brown crystals : mp 266∿268 °C; IR(Nujol) 1760, 1670, 1620 cm^{-1}; MS m/e 380(M^+), 338, 320, 310, 302, 191.

6-Acetoxy-11-hydroxy-1-methoxynaphthacene-5,12-dione(15)

The compound 13(15 mg, 0.04 mmol) was heated under reduced pressure(15 Torr) at 160 °C for 20 min to give 6-acetoxy-11-hydroxy-1-methoxynaphthacene-5,12-dione(15) (14 mg, 100 %) as red crystals : mp 237∿238 °C; IR(Nujol) 1750, 1660; NMR δ 2.60 (3H,s), 4.10(3H,s), 7.00∿8.80(7H,m), 15.55(1H,s, disappeared with D_2O); MS m/e 360(M^+), 320, 302.

Acknowledgment

We thank Mr. K. Kawamura, Mrs. C. Koyanagi, and Miss K. Mushiake, Pharmaceutical Institute, Tohoku University, for spectral measurements and microanalyses.

References

1) Cf. F. Arcamone, Lloydia, 40, 45 (1977).

2) (a) H. Inhoffen, H. Muxfeldt, H. Schaefer, and H. Kramer, Croat. Chem. Acta, 29, 329 (1957); (b) H. Muxfeldt, Angew. Chem., 74, 825 (1962).

3) A.J. Birch and V.H. Powell, Tetrahedron Lett., 3467 (1970).

4) (a) T.R. Kelly, R.N. Goerner, Jr., J.W. Gillard, and B.K. Prazak, Tetrahedron Lett., 3869 (1976); (b) T.R. Kelly, J.W. Gillard, and R.N. Goerner, Jr., Tetrahedron Lett., 3873 (1976); (c) T.R. Kelly, J.W. Gillard, R.N. Goerner, Jr., J.M. Lyding, J. Amer. Chem. Soc., 99, 5513 (1977); (d) T.R. Kelly, Tetrahedron Lett., 1387 (1978); (e) T.R. Kelly and M. Montury, Tetrahedron Lett., 4311 (1978).

5) B.M. Trost, J. Ippen, and W.C. Vladuchick, J. Amer. Chem. Soc., 99, 8116 (1977).

6) R.K. Boeckman, Jr., T.M. Dolak, and K.O. Culos, J. Amer. Chem. Soc., 100, 7098 (1978).

7) L.F. Fieser and J.T. Dunn, J. Amer. Chem. Soc., 59, 1016 (1937).

8) Cf. T.E. Sample, Jr. and L.F. Hatch, Org. Synth., 50, 43 (1970).

9) Isomerization of 4-substituted 1-methoxycyclohexa-1,4-dienes to the corresponding 1,3-dienes in chloroform solution has been studied: S. Takano, S. Yamada, and K. Ogasawara, unpublished results.

10) Y. Ito, T. Konoike, T. Harada, and T. Saegusa, J. Amer. Chem. Soc., 99, 1487 (1977).

11) D. Bethell, G.W. Kenner, and P.J. Powers, J.C.S. Chem. Commun., 227 (1968).

12) H.O. House, J. Amer. Chem. Soc., 77, 5083 (1955).

Received, 13th June, 1979