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Direct Access to 1,4-Dihydroxyanthraquinones: The Hauser Annulation Reexamined with *p*-Quinones

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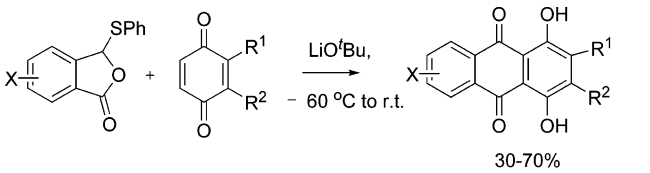
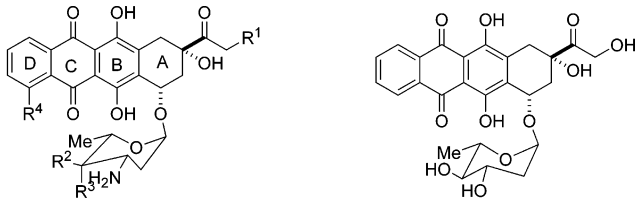


R^1, R^2 = alkyl, O-alkyl, -$(CH_2)_4$-, -$(CH_2)_3$CH(OH)-, -CH=CH-CH=CH-, etc.

3-Phenylsulfanylphthalides (e.g. **8a**) readily react with *p*-benzoquinones in the presence of Li*O*^{t}Bu in THF to furnish 1,4-dihydroxyanthraquinones in good yields and one-pot operations.

1,4-Dihydroxyanthraquinones are common structural subunits of many biologically active quinonoids namely, anthracyclines,[1a] dynemicins,[1b] mitoxantrones,[1c] anthraquinone−steroid hybrids,[1d] and naphthacenedione organic dyes.[1e] Consequently, they serve as useful synthetic intermediates.[1f] They are particularly important for the synthesis of antitumor anthracyclines (e.g. **1** and **2**) that have proved to be the most effective drugs in the treatment of various human tumors for the past 35 years.[1a] An analogue development program has led to the discovery of second generation anthracyclines, including idarubicin (**3**) (Zavedos) and epirubicin (**4**) (Farmorubicin), presently available to medical oncologists. Currently, a few more synthetic analogues, e.g., **5**−**7**, with improved properties are undergoing clinical studies.[2] With a broad objective of developing improved and practicable syntheses of anthracyclines and other quinonoid natural products, we reexamined the Hauser annulation with *p*-quinones. The idea

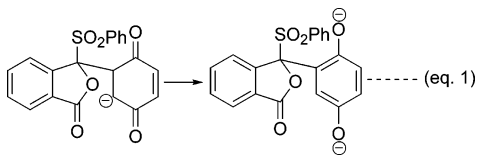


1 R^1= R^2=H, R^3=OH, R^4=OCH_3: Daunorubicin
2 R^1=OH, R^2=H, R^3=OH, R^4= OCH_3: Doxorubicin
3 R^1= R^2= R^4=H, R^3= OH : Idarubicin
4 R^1= R^3=H, R^2=OH, R^4=OCH_3 ; Epirubicin
5 R^1=OH, R^2=H, R^3=$OCH_2C_6H_5$, R^4=OCH_3 ; WP744
6 R^1=OH, R^2=H, R^3=$OCH_2C_6H_5$, R^4=H: WP769

FIGURE 1. Structures of select anthracyclines.

of the reinvestigation stemmed from our past experiences with the reactivity of 3-phenylsulfanylphthalides.[3]

The Hauser annulation[4] is a base-promoted condensation reaction between isobenzofuranones (e.g., **8**) and compounds with polarized multiple bonds to produce quinol-annulated products. It is general, powerful, and regiospecific and has been successfully applied to the total synthesis of quinonoid natural products.[4f] However, this reaction is reported to fail with **8b** and *p*-benzoquinones due to facile aromatization (cf. eq 1) of the initial Michael adducts rendering less reactive phenoxy anions.[5]



In contrast, the corresponding masked quinones (i.e., quinone monoketals) undergo facile annulation to give corresponding anthraquinones and thus serve as the key intermediates in the synthesis of anthracyclines including idarubicin (**3**).[6] Herein, we report successful execution of the title reaction (Scheme 1) for the synthesis of 1,4-dihydroxyanthraquinones.

A few years ago, we demonstrated that 3-phenylsulfanylphthalides (e.g., **8a**) could be excellent annulating agents, if

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(1) (a) (i) Priebe, W. *Anthracycline Antibiotics: New Analogues, Method of Delivery, and Mechanisms of Action*; ACS Symp. Ser. No. 574; American Chemical Society: Washington, DC, 1995. (ii) Arcamone, F. M. *Biochimie* **1998**, *80*, 201−206. (b) Smith, A. L.; Nicolaou, K. C. *J. Med. Chem.* **1996**, *39*, 2103−2117. (c) Faulds, D.; Balfour, J. A.; Chrisp, P.; Langtry, H. D. *Drugs* **1991**, *41*, 400−449. (d) Riccardis, F. D.; Izzo, I.; Filippo, M. D.; Sodano, G. *Tetrahedron* **1997**, *53*, 10871−10882. (e) Sokolyuk, N. T.; Romanov, V. V.; Pisulina, L. P. *Russ. Chem. Rev.* **1993**, *62*, 1005−1024. (f) (i) Kotha, S.; Stoodley, R. J. *Biorg. Med. Chem.* **2002**, *10*, 621−624. (ii) Krohn, K.; Priyono, W. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 339−340.

(2) Fokt, I.; Grynkiewicz, G.; Skibicki, P.; Przewloka, T.; Priebe, W. *Pol. J. Chem.* **2005**, *79*, 349−359.

(3) (a) Majumdar, G.; Pal, R. K.; Murty. K. V. S. N.; Mal, D. *J. Chem. Soc., Perkin. Trans. 1* **1994**, 309. (b) Ghorai, S. K.; Roy, H. N.; Bandopadhyay, M.; Mal, D. *J. Chem. Res. (S)* **1999**, 30. (c) Hauser, F. M.; Dorsch, W. A.; Mal, D. *Org. Lett.* **2002**, *4*, 2237.

(4) (a) Hauser, F. M.; Rhee, R. P. *J. Org. Chem.* **1978**, *43*, 178. (b) Hauser, F. M.; Mal, D. *J. Am. Chem. Soc.* **1983**, *105*, 5688−5690. (c) Hauser, F. M.; Dorsch, W. A. *Org. Lett.* **2003**, *5*, 3753−3754. (d) Patra, A.; Pahari, P.; Ray, S.; Mal, D. *J. Org. Chem.* **2005**, *70*, 9017−9020. (e) Hassner, A.; Stumer, C. *Organic Syntheses Based on Named Reactions*; Elsevier Science: UK, 2002; p 153. (f) Mal, D.; Pahari, P. *Chem. Rev.* **2007**, *107*, 1892−1918.

(5) (a) Russell, R. A.; Warrener, R. N. *J. Chem. Soc., Chem. Commun.* **1981**, 108−110. (b) Majumdar, G.; Murty, K. V. S. N.; Mal, D. *Tetrahedron Lett.* **1994**, *35*, 6139−6140.

(6) (a) Swenton, J. S.; Freskos, J. N.; Morrow, G. W.; Sercel, A. D. *Tetrahedron* **1984**, *40*, 4625−4632. (b) Morrow, G. W.; Swenton, J. S.; Filppi, J. A.; Wolgemuth, R. L. *J. Org. Chem.* **1987**, *49*, 714−719. (c) Bennani, F.; Florent, J.-C.; Koch, M.; Monneret, C. *Tetrahedron Lett.* **1984**, *25*, 3975−3978. (d) Keay, B. A.; Rodrigo, R. *Tetrahedron* **1984**, *40*, 4597−4607. (e) Ge, P.; Russell, R. A. *Tetrahedron* **1997**, *53*, 17477−17488. (f) Achmatowicz, O.; Szechner, B. *J. Org. Chem.* **2003**, *68*, 2398- 2404. (g) Ruano, J. L. G.; Paredes, C. G.; Aleman, J. *ARKIVOC* **2005**, 253−265. (h) Russell, R. A.; Day, A. I.; Pilley, B. A.; Leavy, P. J.; Warrener, R. N. *J. Chem. Soc., Chem. Commun.* **1987**, 1631−1633.

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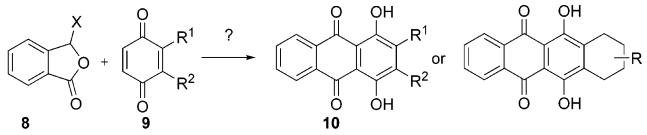
SCHEME 1. Proposed Direct Access to 1,4-Dihydroxy-anthraquinones/6,11- Dihydroxynaphthacenediones



LiO^{t}Bu is used as the base.[3b] This important finding led us to revisit the Hauser annulation with *p*-quinones. It was hoped that the annulation might work out to provide an efficient method for the preparation of biologically active naturally occurring anthraquinones by averting protection−deprotection chemistry. When the yellow anion of **8a**,[3a] generated by treating with lithium *tert*-butoxide in THF at −60 °C, was stirred with a solution of *p*-benzoquinone (**9a**), the reaction turned deep violet, indicating the success of annulation. Indeed, workup of the mixture followed by silica gel chromatographic purification of the crude product provided the desired 1,4-dihydroxyanthraquinone (**10a**) in 56% yield. The structure of this product was confirmed by obtaining a co-NMR spectrum with an authentic sample. In order to discern the effect of the nucleofuges, well-established Hauser donors **8b** and **8c** were separately reacted with *p*-benzoquinone (**9a)** under the conditions for **8a**. The results were very similar to that of entry 1 (Table 1), except that with phthalide sulfone **8b**,[3a] the yield of the annulated product **10a** was much poorer. Having established that **8a** is the best of the annulating agents, we then looked into the effect of nuclear substituents of **8a** on the annulation. As noted in entries 5 and 6 (Table 1), there is no definite trend in the yield, although all of the reactions successfully afforded the respective annulation products **12** and **14**[7] from **11** and **13**.[8]

As the next step, we examined reactivity of **8a** to 2-methyl-*p*-benzoquinone (**9b**)[9] to find if C−C double bonds in the latter are discriminated by the annulation. Their reaction under the conditions described previously furnished the expected annulated anthraquinone **10b**[10] in 65% yield (Table 2). The structure of the product was determined by comparison of the NMR data with the reported data. The product arising out of annulation on C2−C3 double bond was neither detected nor isolated. For further generalization, we extended the study to 2,3-dimethyl-1,4-benzoquinone (**9c**)[11] as the Hauser acceptor. The desired product **10c**[12] was isolated in 69% yield. Similarly, with 2-methoxy-*p*-benzoquinone (**9d**)[11] and 2-(1-hydroxyethyl)-*p*-benzoquinone (**9e**),[13] the products **10d**[14] (67%) and **10e**[15] (43%) were obtained. In both the cases, the annulation took place at the more electrophilic double bonds, i.e., C5−C6 double bonds.

TABLE 1. Annulation of 3-Substituted Phthalides with *p*-Benzoquinone (9a)

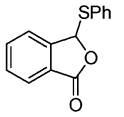
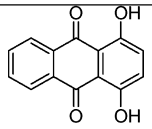
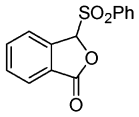
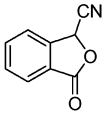
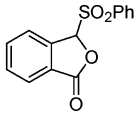
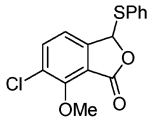
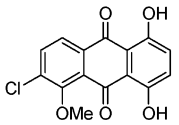
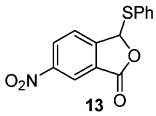
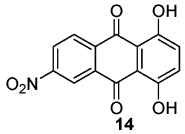
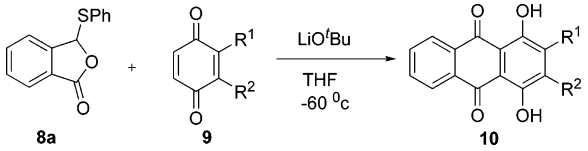
entry	phthalide	base	annulation product	yield
1	 **8a**	LiO^{t}Bu	 **10a**	56%
2	 **8b**	LiO^{t}Bu	**10a**	23%
3	 **8c**	LiO^{t}Bu	**10a**	52%
4	 **8b**	LDA	**10a**	22%
5	 **11**	LiO^{t}Bu	 **12**	57%
6	 **13**	LiO^{t}Bu	 **14**	27%

TABLE 2. Annulation of Phthalide 8a with Substituted *p*-Benzoquinones



entry	quinone	R^1	R^2	product	yield, %
1	**9b**	CH_3	H	**10b**	65
2	**9c**	CH_3	CH_3	**10c**	69
3	**9d**	OCH_3	H	**10d**	67
4	**9e**	$CH(OH)CH_3$	H	**10e**	43

Finally, the reactivities of various naphthoquinones were studied for the entry to tetracyclic systems. As the first example, we chose 5,6,7,8-tetrahydronaphthoquinone (**18**) and adopted the reported procedure[16] for its preparation from 5,6,7,8-tetrahydro-2-naphthol (**15**). Treatment of **15** with ^{t}BuOOH−$RuCl_2(PPh_3)_3$ gave peroxide **16** (Scheme 2). Treatment of **16** with $TiCl_4$ furnished 5,6,7,8-tetrahydro-1,4-naphthalenediol (**17**),[17] contrasting with the original report of formation of **18**. The required quinone **18** could smoothly be prepared by CAN

(7) Satori, G.; Casnati, G.; Bigi, F.; Robles, P. *Tetrahedron Lett.* **1987**, *28*, 1533−1536.
(8) Mal, D.; Patra, A.; Roy, H. *Tetrahedron Lett.* **2004**, *45*, 7895−7898.
(9) Pratt, D. V.; Ruan, F.; Hopkins, P. S. *J. Org. Chem.* **1987**, *52*, 5053−5055.
(10) Simoneau, B.; Brassard, P. *Tetrahedron* **1988**, *44*, 1015−1022.
(11) Ficht, S.; Mulbaier, M.; Giannis, A. *Tetrahedron* **2001**, *57*, 4863−4866.
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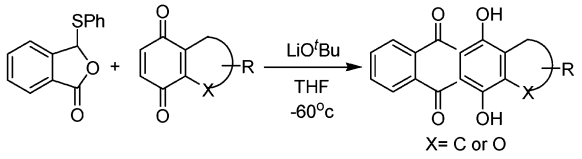
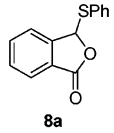
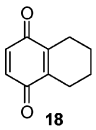
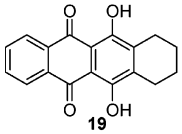
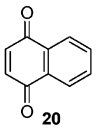
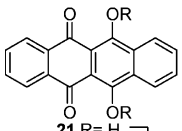
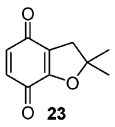
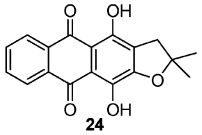
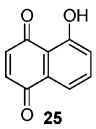
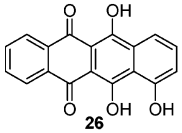
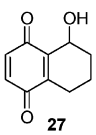
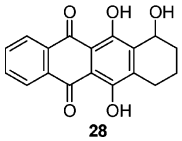
(15) Ge, P.; Russell, R. A. *Tetrahedron* **1997**, *53*, 17469−17476.
(16) Murahashi, S.; Naota, T.; Miyaguchi, N.; Noda, S. *J. Am. Chem. Soc.* **1996**, *118*, 2509−2510.

TABLE 3. Annulation of Phthalide 8a with *p*-Napthoquinones[a]



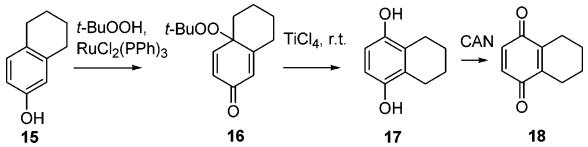
entry	phthalide	quinone	annulation product	yield
1	 **8a**	 **18**	 **19**	66%
2	**8a**	 **20**	 **21** R= H, **22** R= Me	44%
3	**8a**	 **23**	 **24**	66%
4	**8a**	 **25**	 **26**	57%
5	**8a**	 **27**	 **28**	46%

[a] All reactions were carried out in the presence of LiO^{t}Bu.

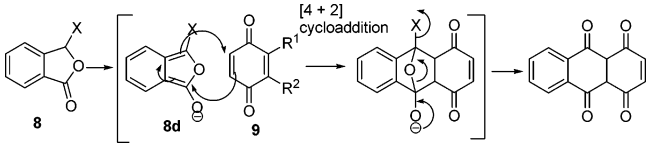
(ceric ammonium nitrate) oxidation of **17**. Annulation of **18** with **8a** under previously described conditions gave dihydroxynaphthacenedione **19**[18] in 66% yield (Table 3). Similarly, annulation of 1,4-naphthoquinone (**20**) gave naphthacenone **21** in 44% yield. It was characterized by its conversion to known dimethyl ether **22**.[19] Annulation of furanoquinone **23**[20] also gave **24** in 66% yield. More interestingly, the annulation with naphthoquinones **25** and **27**[21] proceeded smoothly, although they had free OH groups and the trihydroxy products **26**[22] and **28** were duly characterized. Tolerance of free tertiary OH groups in the quinone monoketals was noted earlier by Swenton et al.[6a,b]

Although we have not carried out detailed mechanistic studies, we propose an alternative mechanism in Scheme 3 to explain

SCHEME 2. Preparation of 5, 6,7,8-Tetrahydro-1,4-naphthoquinone (18)



SCHEME 3. An Alternative Mechanism for the Hauser Annulation



the results presented in the forgoing sections. A concerted [4 + 2] cycloaddition of **8d** with the acceptors may be considered the initial step rather than the Michael addition followed by intramolecular ring closure.[23] This proposal was, in part, corroborated by significant improvement in the yield of **10a** from **8a** (i.e., 56% to 65%), when the anticipated anion of the type **8d** was quenched with TMSCl and then reacted with quinone **9**. Our attempts to trap the anion **8d** (X = SPh) as its *O*-trimethylsilyl ether returned back the starting isobenzofuranone **8a**. Although 3-silyloxyisobenzofuranones are proposed intermediates in many cases, such an intermediate has been characterized in only one instance, by ^{1}H NMR spectroscopy.[24] Usually such intermediates have fleeting existence under ambient conditions.

In conclusion, we have discovered the conditions of the title reaction, which have been elusive for many years. Disclosure of the finding may pave the way for a shorter synthesis of idarubicin (**3**) and the like, in which cases the regiochemical issues are unimportant. Further studies on improving the yields and understanding the mechanism are underway.

Experimental Section

General Annulation Procedure. To a stirred solution of lithium *tert*-butoxide (9.84 mmol) in THF (40 mL) at −60 °C (chloroform/liquid N_2 bath) under an inert atmosphere was added a solution of phthalide (3.28 mmol) in THF (5 mL). The resulting yellowish solution was stirred at −60 °C for 25 min, after which a solution of a Michael acceptor (1.0−1.5 equiv unless otherwise stated) in THF (5 mL) was added to it. The cooling bath was removed after about 1 h and further stirred for 2−6 h. The reaction was then quenched with 10% NH_4Cl (15 mL), the resulting solution was diluted with ethyl acetate (50 mL), and the layers were separated. The aqueous layer was extracted with ethyl acetate (3 × 25 mL). The combined extracts were washed with brine, water, dried (Na_2SO_4), and concentrated. The crude product was purified by column chromatography on silica gel or by recrystallization to get a pure-product.

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6-Chloro-7-methoxy-3-phenylthiophthalide (11). To a stirred solution of 6-chloro-7-methoxy phthalaldehydic acid[25] (200 mg, 0.93 mmol) and *p*-toluenesulfonic acid (10 mg) in dry benzene (5 mL) was added thiophenol (0.2 mL, 1.03 mmol). The mixture was heated at reflux for 2 h with a Dean−Stark apparatus. The reaction mixture was then cooled, and benzene was removed to get a crude solid. It was recrystallized from a mixture of ethyl acetate and petroleum ether to give the pure crystalline product (260 mg, 91%). mp 80−82 °C; IR (KBr) cm^{-1}: 1782, 1752, 1590, 1473, 1049, 943; ^{1}H NMR (200 MHz, $CDCl_3$): δ 7.78 (d, 1H, J = 7.9 Hz), 7.49−7.42 (m, 2H), 7.30−7.20 (m, 4H), 6.62 (s, 1H), 4.00 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 165.6, 154.7, 147.0, 136.4, 134.2, 129.4, 129.1, 129.0, 128.6, 118.7, 118.6, 85.2, 62.8; HRMS *m*/*e* calcd. for $C_{15}H_{12}O_3ClS$ $(MH)^+$ 307.0192, found 307.0154.

5-Methoxy-6-chloro-1,4-dihydroxyanthraquinone (12). mp 190−191 °C; IR (KBr) cm^{-1} 3448, 2948, 2364, 1621, 1457, 1259, 1025, 777; ^{1}H NMR (200 MHz, $CDCl_3$): δ 13.11(s, 1H), 12.83 (s, 1H), 8.16 (d, 1H, J = 8.4 Hz), 7.85 (d, 1H, J = 8.4 Hz), 7.31 (s, 2H), 4.02 (s, 3H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 186.0, 185.6, 157.8, 157.6, 157.0, 138.0, 135.9, 133.8, 130.0, 128.9, 127.1, 124.0, 113.2, 112.1, 61.6; HRMS *m*/*e* calcd. for $C_{15}H_{10}O_5Cl$ $(MH)^+$ 305.0213, found 305.0195.

2,3-Dihydro-2,2-dimethyl-4,11-dihydroxyanthra[2,3-*b*]furan-5,10-dione (24). mp 200−202 °C; IR (KBr) cm^{-1} : 2923, 1725, 1583, 1469, 1259, 1018, 800; ^{1}H NMR (200 MHz, $CDCl_3$): δ 13.55 (s, 1H), 13.01 (s, 1H), 8.34−8.28 (m, 2H), 7.83−7.75 (m, 2H), 3.14 (s, 2H), 1.62 (s, 6H); ^{13}C NMR (50 MHz, $CDCl_3$): δ 187.4, 184.8, 157.2, 156.2, 145.5, 134.4, 133.9, 133.6, 133.2, 126.8, 126.7, 122.3, 113.9, 107.5, 92.2, 40.0, 28.4; HRMS *m*/*e* calcd. for $C_{18}H_{15}O_5$ $(MH)^+$ 311.0919, found 311.0886.

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Supporting Information Available: Preparation of starting quinones, preparation of **17** and **18**, and characterization data for **9b**−**e**, **10a**−**e**, **13, 14**, **17**, **18**, **19**, **21**, **22**, **23**, **26**, **27**, **28**, **29**. This material is available free of charge via the Internet at http://pubs.acs.org.

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