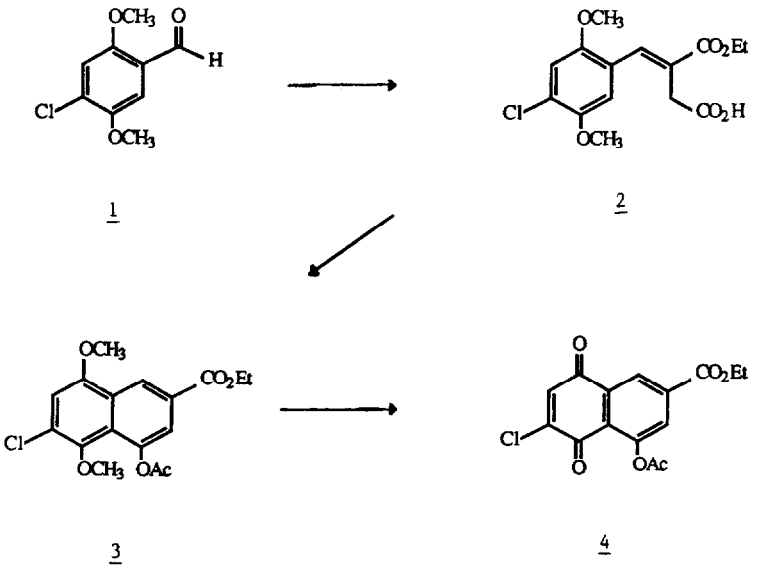
Tetrahedron Letters,Vol.30,No.10,pp 1201-1204,1989 0040-4039/89 $3.00 + .00
Printed in Great Britain Pergamon Press plc

AN EFFICIENT ROUTE TO 3-CHLOROJUGLONES

James L. Bloomer* and Joseph A. Gazzillo
Department of Chemistry, Temple University, Philadelphia PA 19122 USA

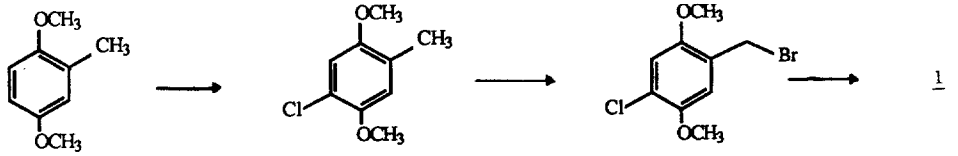
Summary: The novel 4-chloro-2,5-dimethoxybenzaldehyde 1 has been prepared and converted in only three steps to 5-acetoxy-7-carboethoxy-3-chloro-1,4-naphthaquinone 4. Subsequent Diels-Alder reaction affords a tetracyclic enol ether 9 in a regiospecific manner.

Failure of simple juglones to undergo regiospecific reaction in the Diels-Alder synthesis of anthracyclines and other natural products has led to the development of 3-halojuglones for that purpose[1]. The present communication describes the preparation of the novel chloroaldehyde 1 and its conversion in only three steps to the chlorojuglone derivative 4.



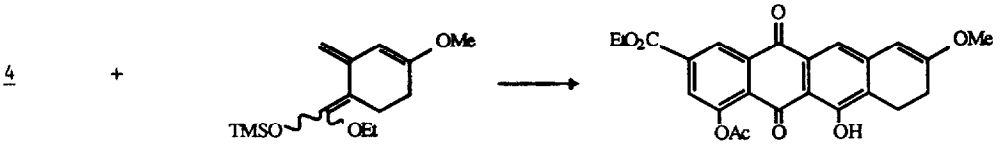
Treatment of the aldehyde 1 with diethyl succinate, sodium hydride, and a catalytic amount of ethanol in benzene afforded the aralkenoic acid 2 as an oil (64%), which could be taken directly for cyclization with acetic anhydride and sodium acetate[2] to provide the bicyclic naphthoate ester 3[3] m.p. 155.0-155.5 °C (68%). The concomitant demethylation and oxidation of the bicyclic ester 3 was achieved using ceric ammonium nitrate in 90% acetic acid (conditions previously applied to the oxidation of aromatic methyl groups to the aldehyde function)[4] to give 57% of the chlorojuglone acetate 4[5] m.p. 125-135°C. (dec.)

The aldehyde synthon 1 was prepared as follows: Commercially available 2-methylhydroquinone was treated with dimethyl sulfate in alkaline solution containing sodium hydrosulfite to afford the known dimethyl ether 5[6], which was subsequently chlorinated with sulfuryl chloride to yield the known chloro derivative 6[7]. Treatment of the latter with N-bromosuccinimide in refluxing carbon tetrachloride containing dibenzoyl peroxide afforded the benzylic bromide 7[8] m.p. 99.5-100.5°C (in 68% yield after recrystallization from high boiling petroleum ether) which exhibited ^{1}H NMR 4.50 (s,2H)[9]. The benzylic bromide 7 was converted to the key aldehyde synthon 1 m.p. 112-114°C (63%) which exhibited ^{1}H NMR 10.39 (s,1H)[10] and IR 1690 cm^{-1} via unexceptional Sommelet conditions[11].



5 6 7

The chlorojuglone 4 reacts regiospecifically in the Diels-Alder reaction with the diene 8. The diene 8 was prepared by the method of Gesson and reacted under conditions reported by that author for the bromojuglone series[12] to provide a Ring D-functionalized tetracyclic enol ether 9 m.p. 236-237°C (46%) as a brick-red powder with UV-VIS 214 (5.11) 263sh, 313 (4.71), 448 (4.58), IR 1772 (acetoxy), 1724 (ArCOOR), 1676 cm^{-1}(quinone) ^{1}H NMR 12.85 (s,1H), 8.79 (d,1H J=1.5 Hz), 7.99 (d,1H J=1.5Hz), 7.39 (s,1H) 5.61 (s,1H), 5.61 (s,1H), 4.46 (q,2H J=7Hz), 3.78 (s,3H), 2.99 (t,2H J=2Hz) 2.47 (t,2H J=2Hz), 1.45 (t,3H J=7Hz).



8 9

The tetracyclic enol ether 9 is potentially useful for the synthesis of Ring D-modified anthracyclines[13].

In summary, the Stobbe condensation-acetic anhydride cyclization-CAN oxidation sequence represents a short and efficient route from aromatic aldehydes to juglone derivatives. Moreover, modifications of the carbonyl and succinate synthons in the Stobbe condensation should allow the preparation of bicyclic materials capable of regiospecific elaboration into further rings at both ends of the molecule to provide either linear or nonlinear tetracyclic arrays. Model studies are currently in progress[14].

Acknowledgement: We wish to thank Professor Gesson for details of the diene preparation prior to publication.

References and Notes

1.) For application of 3-bromojuglone derivatives to the synthesis of 11-deoxydaunomycin, see J. P. Gesson, J. C. Jacquesy and M. Mondon, Nouv. J. Chim. 7, 205-211 (1983). The synthetic concept has more recently been extended to a series of Ring D methoxy regioisomers of 11-deoxydaunomycin. See J. P. Gesson, A. A. Abdallah, J. C. Jacquesy, and M. Mondon, Bull. Soc. Chim. Fr. 1986, 93-100 (1986). The 3-chlorojuglone series has been used,e.g., in the synthesis of chrysophanol via vinylketene acetals. See J. Savard and P. Brassard, Tetrahedron Lett. 4911-4914 (1979).

2.) 2-methoxybenzaldehyde was condensed with diethyl methylsuccinate and cyclized similarly. See J. W. Loder, S. Mongolsuk, A. Robertson, and W. B. Whalley, J. Chem. Soc. 2233-2237 (1957).

3.) IR: 1760 (aromatic acetate) 1700 cm^{-1}(aromatic ester).
^1H NMR 8.91 (s,1H), 7.81 (s,1H), 6.87 (s,1H), 4.42 (q,2H, J=7Hz), 4.01 (s,3H), 1.41 (t,3H, J=7Hz).
NOTE: all ^1H NMR data are delta values in $CDCl_3$.
UV: 208 (4.67), 238 (4.72), 294sh, 309 (3.89), 328sh, 343 (4.02).
NOTE: All UV and UV-VIS spectra are given as lambda max (log epsilon) in 95% ethanol.

4.) We originally used the conditions reported for aromatic methyl oxidation given by L. Syper, Tetrahedron Lett. 4493-4496 (1966) in an attempt to convert the toluene 6 directly into benzaldehyde 1. Failure of that reaction led to its application to the 1,4-dimethoxy derivative 3 for quinone formation. More recently, high yields of quinones from 1,4-dimethoxy derivatives have been reported by L. Syper, K. Kloc, J. Mlochowski, and S. Szulc, Synthesis 1979 521-522 (1979), using pyridine 2,6-dicarboxylic acid as catalyst.

5.) IR: 1775 (ArOCOR) 1715 (ArCOOR) and 1760 cm^{-1} (quinone).
^1H NMR 8.62 (s,1H), 7.99 (s,1H), 7.22 (s,1H), 4.40 (q,2H, J=7Hz) 2.40 (s,3H), 1.35 (t,3H, J=7Hz).
UV: 204 (4.78), 234 (4.38), 251sh, 270 (4.28), 345 (4.09).

6.) R. Nietzki, Liebigs Annalen 215, 125-172 (1882). Addition of a few mole percent of sodium hydrosulfite prevented the rapid oxidation of the hydroquinone dianion.

7.) The ring-chlorinated compound was obtained as one of the products in the benzoyl peroxide-catalyzed chlorination of the diemthoxytoluene 5 using 1,3-dichloro-5,5-dimethylhydantoin. J. Green, D. McHale, S. Marcinkiewicz, D. Mamalis, and P. R. Watt, J. Chem. Soc. 3362-3373 (1959).

8.) CAUTION: LACHRYMATOR AND IRRITANT.

9.) Also 6.95 (s,2H), 3.90 (s,3H), and 3.88 (s,3H).

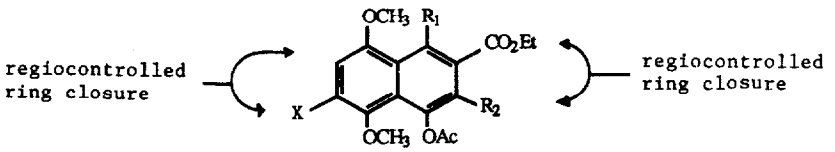
10.) Also 7.38 (2,1H), 7.07 (s,1H), and 3.91 (s,6H) (Both methoxyls).

11.) S. J. Angyal, Org. Reactions 8, 197-217 (1954). See p. 210. We used the conditions reported for the Sommelet reaction on 4-nitro-1-chloromethylbenzene and obtained a 63% yield of aldehyde.

12.) J. P. Gesson, J. C. Jacquesy and M. Mondon, Nouv. J. Chim. 1983, 205-221 (1983).

13.) Our original intent was to convert the aromatic ester function to the hydrazide, apply the Curtius reaction, and then access a variety of functional groups via diazonium chemistry.

14.) Our synthetic strategy appears to hold considerable promise for the regiocontrolled construction of polycyclic arrays. As a model compound for regiospecific ring closure, we have prepared the following system where X=R_1=H and R_2=CH_3 by the use of diethyl methylsuccinate in the Stobbe condensation. This type of compound should be capable of



elaboration into a linear tricyclic system using chemistry developed by F. M. Hauser and R. P. Rhee, J. Org. Chem. 43, 178-80 (1978) in which ethyl 2-methylbenzoate was treated with NBS, thiophenoxide anion, the thiophenol oxidized to the sulfoxide, and the resultant sulfoxyl ester condensed with acrylic or crotonic esters to produce an additional aromatic ring. Alternative chemistry using the dianion of 2-methylbenzoic acid was also described by F. M. Hauser and R. P. Rhee, J. Amer. Chem. Soc. 99, 4533-4534 (1977). Extension of our studies to the series X=Cl could provide a bicyclic synthon capable of regiocontrolled elaboration at both ends to provide a linear tetracyclic array. Substitution of an aromatic ketone in the Stobbe to give substitution at R_1 would likewise potentially access the bent tricyclic and tetracyclic arrays similarly.

(Received in USA 20 October 1988)