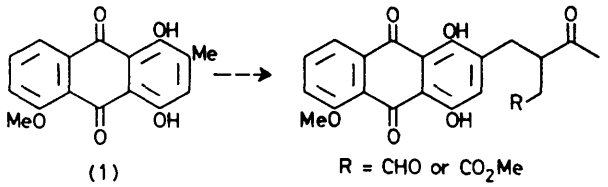
Regiospecific Syntheses of Islandicin and Digitopurpone Monomethyl Ethers

By ROBERT D. GLEIM, STEVEN TRENBEATH, FUMIO SUZUKI, and CHARLES J. SIH*
(*School of Pharmacy, University of Wisconsin, Madison, Wisconsin* 73706)

Summary Regiospecific methods for the preparation of islandicin and digitopurpone monomethyl ethers, the tricyclic precursors of daunomycinone and adriamycinone, are described.

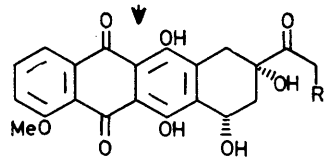
RECENTLY, we developed base-catalysed cyclization methods for the conversion of dihydroanthraquinone derivatives into anthracyclinones.[1] Applications of these model reactions to the synthesis of tetracyclic precursors of daunomycinone (**2**) and adriamycinone (**3**), the aglycones

of the clinically useful anthracycline antibiotics daunorubicin[2] and adriamycin,[3] require suitably substituted tricyclic intermediates, notably, islandicin methyl ether (**1**). We now report the regiospecific syntheses of the unsymmetrically substituted anthraquinones, (**1**) and (**12**).



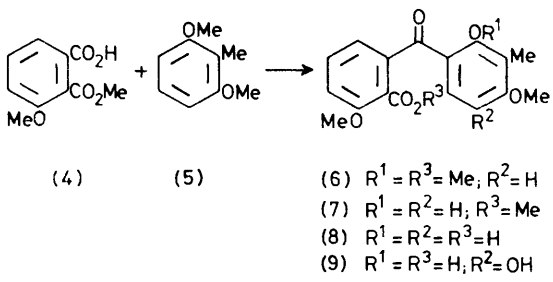
(1)

R = CHO or CO_2Me



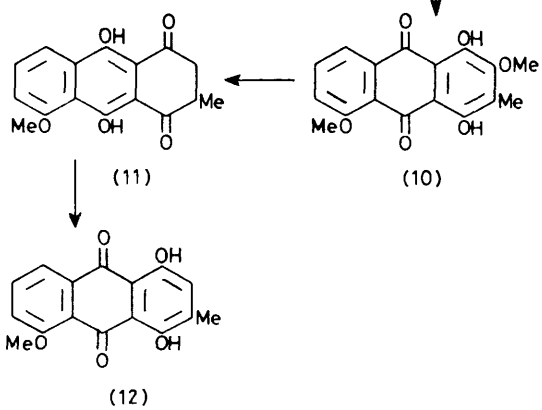
(2) R = H
(3) R = OH

Condensation of 2,6-dimethoxytoluene (**5**) with 3-methoxy-2-methoxycarbonylbenzoic acid[4] (**4**) in trifluoroacetic anhydride (25 °C, 40 min) afforded the diaryl ketone (**6**) (84%, m.p. 136—138 °C), which was selectively demethylated ($AlCl_3$–CH_2Cl_2, 15 °C, 45 min) to yield (**7**) (97%, m.p. 156—157 °C) which was then saponified (8% NaOH, 70 °C, 30 min) to (**8**) (95%, m.p. 259—261 °C decomp.). Elbs oxidation[5] of (**8**) afforded (**9**) [45 and 20% of unchanged (**8**), m.p. 235 °C (decomp.)]. Cyclization of (**9**) with conc. H_2SO_4 (25 °C, 1 h) yielded exclusively (**10**) (87%, m.p. 201—202 °C). Treatment of (**10**) with Zn metal in HOAc gave the dihydroanthraquinone derivative[6] (**11**), which was easily oxidized (aerially) by heating in HOAc–NaOAc at 110 °C (4 h) to give (**12**), m.p. 209—211 °C [60% from (**10**)]. Demethylation of (**12**) with $AlCl_3$ led to a compound whose physical properties were consistent with those of digitopurone,[7] but clearly different from those of natural islandicin.[8]



(4) (5)

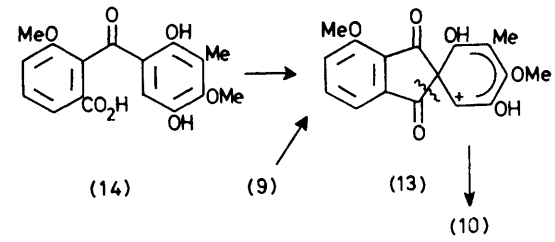
(6) $R^1 = R^3 = Me$; $R^2 = H$
(7) $R^1 = R^2 = H$; $R^3 = Me$
(8) $R^1 = R^2 = R^3 = H$
(9) $R^1 = R^3 = H$; $R^2 = OH$



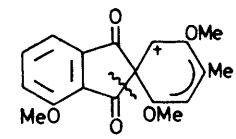
(11) (10)

(12)

This result may be rationalized by an easy Hayashi rearrangement[9] of (**9**) during H_2SO_4 cyclization, presumably through the spirocyclic intermediate,[10] (**13**), as the isomeric arylbenzoic acid,† (**14**), m.p. 235—236 °C (decomp.), also gave exclusively (**10**) upon reaction with H_2SO_4. Thus, it appeared that the requisite acylium ion was generated *via* the apparent scission of the carbonyl bond β to the methoxy in the phthalide unit of (**13**).



(14) (9) (13) (10)

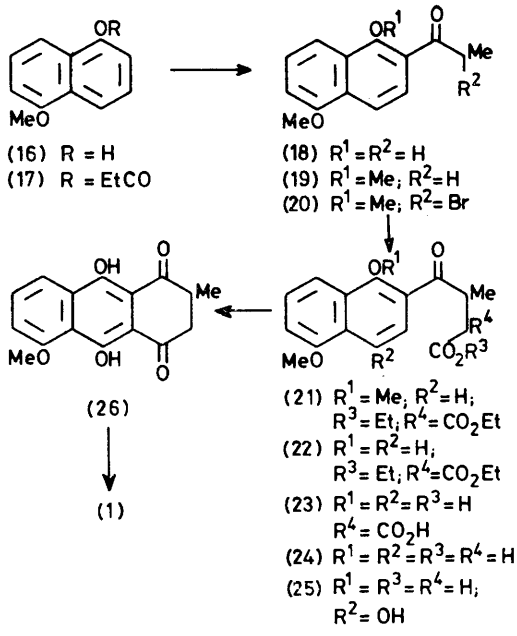


(15)

Although such rearrangement had been encountered earlier, Kende[7] apparently observed the cleavage of the carbonyl bond α to the methoxy in the spirocyclic intermediate (**15**).

This unexpected rearrangement in the final cyclization step led us to abandon this approach and an alternative synthesis of (**1**) from 1-hydroxy-5-methoxynaphthalene[11] (**16**) was devised. Acylation [$(EtCO)_2O$–C_5H_5N] of (**16**) afforded (**17**) (92%), which underwent a Fries-type rearrangement upon treatment with BF_3–Et_2O (120 °C, 1 h) to yield (**18**) (80%), m.p. 92—95 °C. After methylation (Me_2SO_4–K_2CO_3–HOAc, 4 h), (**19**) was brominated (pyridine hydrobromide perbromide–tetrahydrofuran, 1 h) to give (**20**) (79%). Alkylation [$CH_2(CO_2Et)_2$–NaH–dimethylformamide–hexamethylphosphoric triamide, 6 h, 25 °C] of (**20**) yielded (**21**) (90%), which upon demethylation ($AlCl_3$–CH_2Cl_2, 8 h) gave (**22**) (86%), m.p. 96—98 °C. Alkaline

† The arylbenzoic acid (**14**) was synthesized *via* a similar sequence of reactions except the isomeric 2-methoxy-6-methoxycarbonyl benzoic acid was used instead of (**4**).



hydrolysis (1M KOH, 6 h, 70 °C) of (**22**) afforded the dibasic acid (**23**) (85%), m.p. 190—191 °C, which was decarboxylated (C_5H_5N, 110 °C, 1 h) to yield (**24**) (98%), m.p. 167—168 °C. Elbs oxidation[5] of (**24**) gave (**25**) (48%), m.p. 196—197 °C. Although HF (25 °C) and polyphosphoric acid (100 °C) failed to transform (**25**) into (**1**), cyclization of (**25**) was achieved using conc. H_2SO_4 (1 h, 50 °C), presumably *via* the unstable intermediate (**26**), which upon oxidation and tautomerization gave exclusively (**1**)‡ (30%), m.p. 194—195 °C. No trace of (**12**) was detectable in the reaction mixture.

The successful completion of a regiospecific synthesis of (**1**) is a further step in the preparation of tetracyclic precursors of adriamycinone. Further, this scheme should allow the ready synthesis of other unsymmetrically substituted anthraquinone derivatives, which may serve as more suitable precursors to adriamycinone, *via* alkylation of the intermediate (**20**).§

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‡ Methylislandicin can be readily distinguished from methyldigitopurpone *via* t.l.c. using three developments in the solvent system EtOAc-benzene (2:98).

§ All intermediates gave satisfactory C, H analyses and/or mass spectra; i.r. and n.m.r. spectra are consistent with the assigned structures. The yield reported was unoptimized and m.p.s were uncorrected.

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