

## A VERSATILE SYNTHESIS OF HYDROXY-9,10-ANTHRAQUINONE-2-CARBOXYLIC ACIDS.

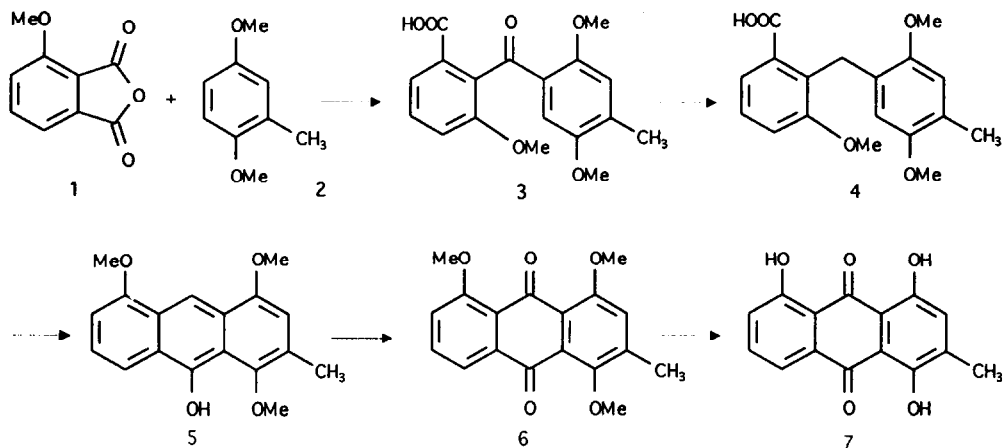
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**Abstract** : Islandicin, a mould metabolite, can be synthesised in a few, robust, high yielding steps. This procedure can be further elaborated to give a variety of hydroxy-9,10-anthraquinone-2-carboxylic acids.

A large number of syntheses of islandicin **7**<sup>1</sup> abound in the literature, but these frequently require a large number of synthetic steps and are often low yielding, allowing only small quantities of this important mould metabolite<sup>2</sup> to be available. A synthetic route (Scheme 1) was envisaged which could give **7** on a reasonable scale, in only six steps and, in addition, could also allow the use of an anthrol intermediate **5** to give 1,4,5,-trihydroxy-9,10-anthraquinone-2-carboxylic acid **9** a novel analogue of rhein<sup>3</sup> (4,5-dihydroxy-9,10-anthraquinone-2-carboxylic acid) a compound of some interest to us. Contrary to some published opinion, *e.g.* Johnson *et al.*<sup>4</sup> and Snieckus *et al.*<sup>5</sup> but according to Kende *et al.*<sup>6</sup> a regiospecific Friedel-Crafts reaction, using standard conditions, between 3-methoxyphthalic anhydride **1**<sup>7,8</sup> and 2,5-dimethoxymethylbenzene **2**<sup>9</sup> to give 2-(2,5-dimethoxy-4-methylbenzoyl)-3-methoxybenzoic acid **3** is possible. We have confirmed this result and found that this important intermediate can be synthesised on a multigram scale in 72% yield, using AlCl<sub>3</sub> with dichloromethane as solvent, at ambient temperature. Only one positional isomer was isolated, mp 190°C (lit.<sup>5,6</sup> 201°C and 183-185°C *respec.*).

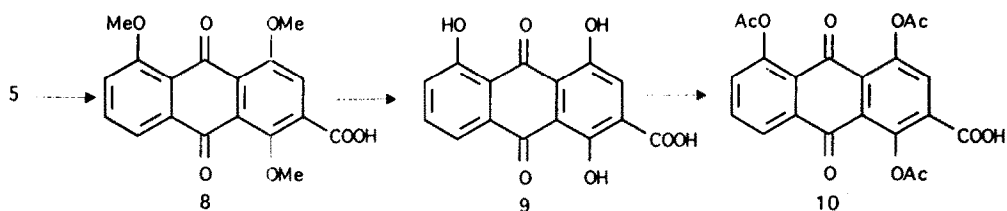
**Scheme 1**



The ketonic carbonyl group of **3** had to be reduced so as to avoid the known isomerising Hayashi rearrangement<sup>6,10</sup> which would occur if it were subjected to Friedel-Crafts conditions. This was successfully achieved by applying "ionic hydrogenation" conditions<sup>11</sup>, *i.e.* triethylsilane and trifluoroacetic acid (TFA), to this compound to give the benzyl-benzoic acid **4** in 80% yield, mp 207°C (lit.<sup>6</sup> 191-192°C). Ring closure of **4** using 50% TFA and 50% trifluoroacetic anhydride<sup>4</sup> afforded **5** (and some anthrone tautomer) in 84% yield, mp 178°C (lit.<sup>5</sup> 173°C). Oxidation to quinone **6** was best achieved using copper(II)nitrate supported on silica<sup>12</sup> in 50% yield, mp 161°C (lit.<sup>5</sup> 162°C). Compound **6** was readily demethylated by subjecting it to molten pyridine hydrochloride<sup>5</sup> at 180°C, giving islandicin **7** in 52% yield, mp 217°C (lit.<sup>2,13</sup> 216-218°C).

When a suspension of **5** in aqueous potassium permanganate and 2-methyl-2-propanol was heated, under reflux, for 24hr, filtered, evaporated (some by-product **6** washed out with chloroform) and the residue, which had been dissolved in water, was acidified, the doubly oxidised yellow 1,4,5-trimethoxy-9,10-anthraquinone-2-carboxylic acid **8** was obtained in 33% yield, mp 220-223°C (Scheme 2). Compound **8** was subjected to boiling 45% HBr in acetic acid for 1 hr, then quenched in water, whereupon an intense purple precipitate of the trihydroxy acid **9** was deposited. This impure product was dissolved in 2M NaOH, filtered and reacidified. The yield of pure acid (mp >260°C) was 73%. Quantitative acetylation of **9**, to give 1,4,5-triacetoxy-9,10-anthraquinone-2-carboxylic acid **10**, mp 179-180°C, was achieved by refluxing it in acetic anhydride to which a few drops of a solution of H<sub>2</sub>SO<sub>4</sub>/acetic acid (1:1) had been added. After 0.5 hr the solution was quenched in ice/water and the suspension heated to break down any mixed anhydride present. It was then cooled and filtered.

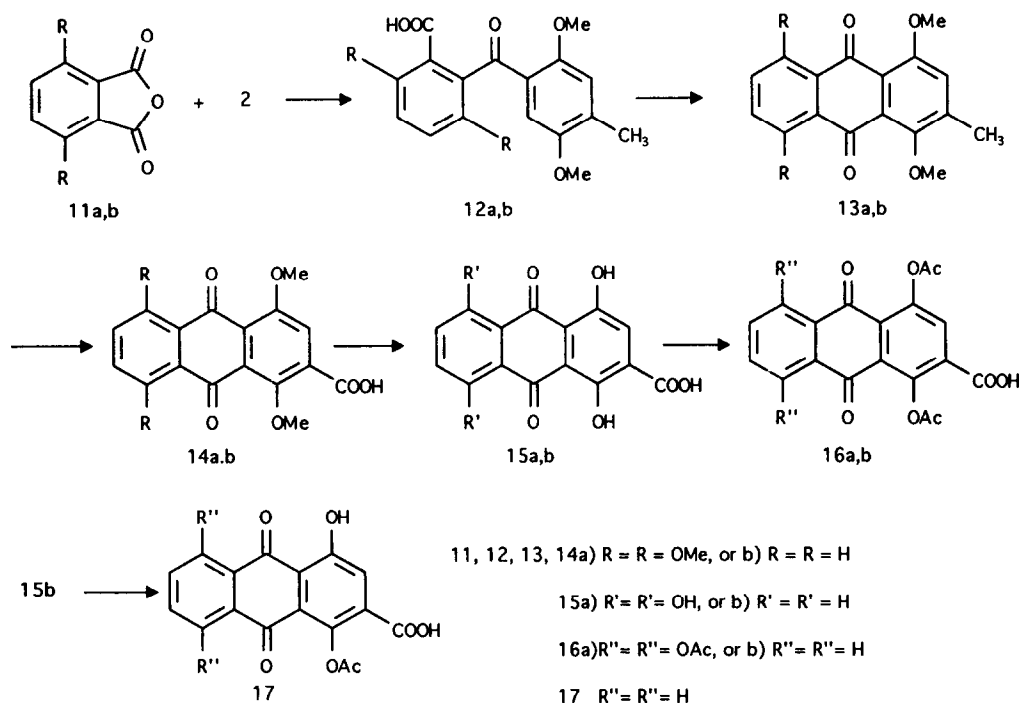
### Scheme 2



This synthetic sequence can be used to give other examples of hydroxy-9,10-anthraquinone-2-carboxylic acids, and when Hayashi rearrangement is unimportant it can be significantly simplified (Scheme 3). For example a Friedel-Crafts reaction to give **12a** or **12b** proceeded smoothly using AlCl<sub>3</sub> and CH<sub>2</sub>Cl<sub>2</sub> (or ClCH<sub>2</sub>CH<sub>2</sub>Cl) giving a yield of 67%, mp 151°C and 69%, mp 141°C respectively. Anhydride **11a**, the precursor to **12a**, was synthesised using an improved method to that described by Krapcho *et al.*<sup>14</sup> Interestingly **12a** was found to be a mixture of rotamers.<sup>15</sup> Ring closure to give **13a** or **13b** was best achieved by stirring in concentrated H<sub>2</sub>SO<sub>4</sub> for 1hr at ambient temperature, quenching in water and extracting into CHCl<sub>3</sub>. Some demethylation was apparent, but the isolated materials could be readily remethylated by refluxing them in 2-butanone containing

dimethyl sulphate and potassium carbonate. Yields were 91% and 84% respectively; mps were 241.5-242.5°C (lit.<sup>5</sup> 239°C) and 132°C (lit.<sup>16</sup> 131-132°C). Oxidation with potassium permanganate *etc.*, gave yellow **14a** in 52% yield, mp 236-238°C, and yellow **14b** in 47% yield, mp 192-194°C respectively. Demethylation of **14a** in boiling HBr-acetic acid afforded a black solid, **15a**, in 86% yield, mp >260°C, whilst **14b** gave a dark red solid, **15b**, in 64% yield, mp 249-250°C. Once compound **15a** was acetylated and quenched in water it afforded a gum which was triturated in warm aqueous acetic acid to give **16a** in 75% yield, mp 209-211°C. Compound **15b** when similarly treated (acetylation time = 1.5hr) afforded only monoacetylated product **17**<sup>17</sup> in 29% yield, mp 163-165°C. However complete acetylation of **15b** to give **16b**, in quantitative yield (mp 174-176°C) was possible when the reaction time was extended to 24hr. This unusual example of regioselectivity presents an interesting insight into the acetylation of hydroxy-9,10-anthraquinone-2-carboxylic acids, especially when taking into account the ready tendency of these species to form mixed anhydrides with acetic anhydride.

Scheme 3



#### Acknowledgements:

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## References and notes:

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- 9 Gripenberg J. and Hase T., *Acta Chem. Scand.*, **1963**, *17*(8), 2250-2252. An improved method was to react 2,5-dihydroxy-2-methylbenzene in 2-butanone with dimethyl sulphate and  $K_2CO_3$  for 24hr, the residue obtained after filtration & evaporation (94% yield) could be used without further purification.
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- 14 Krapcho A. P., Petry M. E. and Hacker M. P., *J. Med. Chem.*, **1990**, *33*(9), 2651-2655. This synthesis has been improved by hydrolysing the dimethylated 2,3-dicyanohydroquinone with NaOH, acidifying, then heating the isolated phthalic acid in pyridine/acetic anhydride.
- 15  $^1H$  nmr analysis of **12a** ( $CDCl_3$ , 30°C) appeared to indicate that a mixture of two slowly interconverting rotamers about the C-C=O bond was present in a *c.a.* 2:1 ratio. Using a combination of 2D EXSY (Perrin C. L. and Dwyer T. J., *Chem. Rev.*, **1990**, *90*, 935-967) to connect exchange related signals, and 1D nOe's, it was possible to assign, unambiguously, signals H-3, H-6,  $CH_3O-2$  and  $CH_3O-5$  on the R. H. side of the structure. These were 6.82 $\delta$  (6.67 $\delta$ ), 6.32 $\delta$  (7.58 $\delta$ ), 3.92 $\delta$  (3.41 $\delta$ ) and 3.55 $\delta$  (3.87 $\delta$ ) respectively (the minor rotamer signals are in brackets). Variable temperature nmr studies in DMSO showed a trend of coalescence tending toward sharpness of the rotamer signals, such that at 120°C only the R. H. nucleus signals H-6, and  $CH_3O-5$  still showed appreciable broadening.
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- 17 Acetylation of the OH-1 substituent on **17** was confirmed by nOe difference spectroscopy. A nOe was observed at the H-3 proton upon irradiation of the lowfield OH proton at 12.7 $\delta$ , indicating that the OH and H-3 protons are adjacent to each other. Furthermore no nOe's are observed upon irradiation of the OAc methyl protons, as expected.