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An expedient and efficient synthetic route to some naturally occurring polyfunctional naphthazarins

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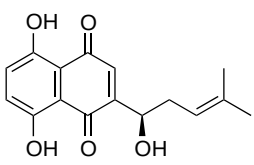
Abstract—A concise and versatile route to functionalised naphthazarins via 1,3,4,5,6,8-hexamethoxynaphthalene is described and is illustrated with the synthesis of three natural products, aureoquinone, boryquinone and 3-ethyl-2,7-dihydroxynaphthazarin.

A large number of natural products containing the 1,4-naphthoquinone moiety have been isolated and characterised.[1] Such compounds have been found in a variety of organisms including lichens, fungi, echinoids and higher plants. An interesting sub-group of naphthoquinones is the 5,8-dihydroxy-1,4-naphthoquinones, known as naphthazarins. A number of naphthazarins, such as shikonin (**1**),[2] hybocarpone (**2**)[3] and aureoquinone (**3**),[4] display potent biological properties including potent cytotoxicity as well as antibacterial and anti-inflammatory properties.

As part of our continuing interest in naphthoquinone-based natural products, we embarked on a programme designed to readily access highly oxygenated naphthoquinones via a versatile and expedient synthetic route. More particularly, we demonstrate the versatility of our route by targeting two known naphthazarins, aureoquinone (**3**) and 3-ethyl-2,7-dihydroxynapthazarin (**4**).[5] In this communication we also describe the *first* unambiguous identification of boryquinone (**5**), a naphthoquinone isolated from the lichen *Cladonia boryi* Tuck.,[6] through chemical synthesis.

Our synthesis (Scheme 1) commenced with the readily available 2,5,7-trimethoxy-1,4-naphthoquinone (**6**)[7] which was reductively methylated with sodium dithionite and dimethyl sulphate under basic phase-transfer conditions to yield naphthalene **7** in 81% yield.† Selective formulation of **7** under standard Vilsmeier conditions gave the desired naphthalene **8** as is indicated by the presence of an aldehydic proton at 10.45 ppm. In order to install the hydroxy functionality required for the synthesis of naphthazarins, a Baeyer–Villiger oxidation was attempted on **8**. Surprisingly, none of the desired product was obtained and unreacted starting material was recovered quantitatively. After much experimentation, a one-pot rearrangement and in situ oxidation of the naphthalene **8** with acidic hydrogen peroxide gave the naphthoquinone **9**[8] in 72% yield. Reductive methylation of the naphthoquinone **9** as described above gave the desired symmetrical naphthalene **10**, our key synthetic intermediate.[9] With this precursor in hand, we were able to selectively *C*-functionalise the remaining nuclear positions of the ring systems.



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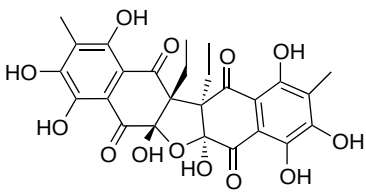

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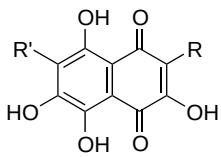

(3) R=R'=Me
(4) R=Et, R'=H
(5) R=Et, R'=Me

Keywords: naphthalenes; natural products; quinones.
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† All new compounds gave satisfactory spectroscopic and analytical data.

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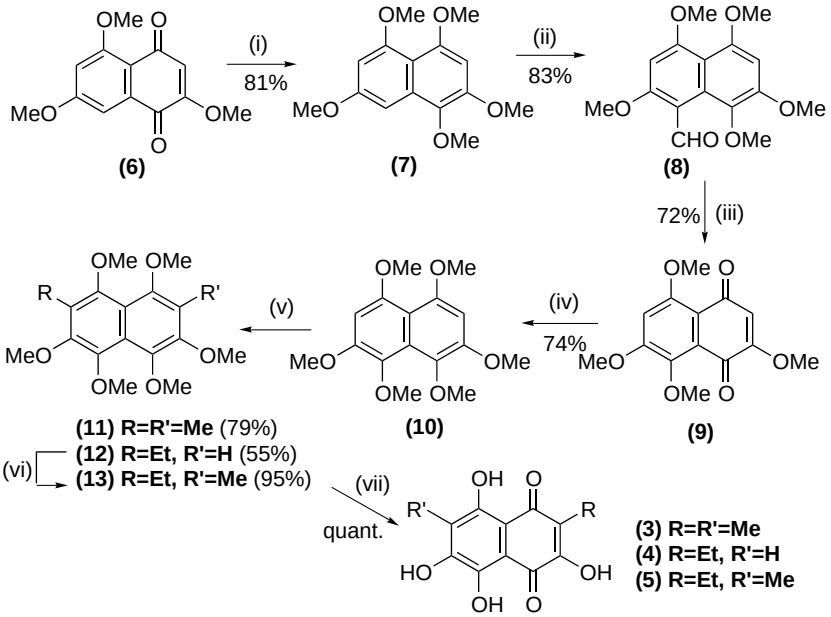

Scheme 1. *Reagents and conditions*: (i) excess sodium dithionite, dimethyl sulphate, KOH, NBu_4Br in water/THF, 18 h; (ii) 5 equiv. $POCl_3$, 4 equiv. DMF in DCM, 0°C at 30 min then rt for 18 h; (iii) 10-fold excess H_2O_2, cat. H_2SO_4 in MeOH, 90 min at rt; (iv) excess sodium dithionite, dimethyl sulphate, KOH, NBu_4Br in water/THF, 18 h; (v) for (**11**), 4.5 equiv. BuLi, 4.5 equiv. TMEDA, THF, −78°C, 30 min, then excess MeI, −78°C to rt, 30 min; for (**12**), 1.2 equiv. BuLi, 1.2 equiv. TMEDA, THF, −78°C, 30 min, then excess EtI, −78°C to rt, 30 min; (vi) 1.2 equiv. BuLi, 1.2 equiv. TMEDA, THF, −78°C, 30 min, then excess MeI, −78°C to rt, 30 min; (vii) 5 equiv. BBr_3, DCM, −78°C to rt, 48 h.

Our initial attempts at the *C*-functionalisation of the naphthalene **10** utilised organolithium bases (*n*-BuLi, *tert*-BuLi and LICKOR) in the presence of the appropriate alkyl halide but no alkylation product was observed. The presence of tetramethylethylenediamine (TMEDA) was later found to be crucial to the success of the alkylation reactions. Hence, treatment of naphthalene **10** with 4.5 molar equivalents of *n*-BuLi and TMEDA directly gave the naphthalene **11** in 79% yield. Subsequent demethylation with boron tribromide and in situ oxidation gave a red solid with identical physical and spectroscopic properties to aureoquinone (**3**), a new protease inhibitor isolated from *Aureobasidium* sp.[4]

Treatment of naphthalene **10** with 1.2 molar equivalents of *n*-BuLi, TMEDA and excess ethyl iodide gave a mixture of starting material: mono-alkylated: dialkylated products in the ratio of 1:2.7:1.2. The monoalkylated product **12** was isolated in 55% yield and subsequent demethylation followed by aerial oxidation gave 3-ethyl-2,7-dihydroxynaphthazarin (**4**), consistent with literature data.[5]

Further alkylation of naphthalene **12** with methyl iodide and 1.2 molar equivalents of *n*-BuLi and TMEDA gave the unsymmetrical naphthalene **13** as characterised by the NMR spectroscopic data. Demethylation and aerial oxidation gave the naphthazarin **5**. From the physical, spectroscopic and HPLC analysis, this synthetic sample was found to be identical in all respects to the naturally occurring naphthoquinone boryquinone, detected in extracts from the thallus tips of the lichen *Cladonia boryi* Tuck.[6] This is the first unambiguous identification of the structure of boryquinone. Interestingly, boryquinone (**5**) is also present in extracts of the cultured mycobiont of *Lecanora hybocarpa* (Tuck.) Brodo, and suggests that this may be the biosynthetic precursor of hybocarpone (**2**),[3] a novel bis-naphthazarin derived pentacycle.

Acknowledgements

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9. Selected data for naphthalene **10**: ^{1}H NMR ($CDCl_3$): δ 3.79 (6H, s, 2×OMe); 3.91 (6H, s, 2×OMe); 3.95 (6H, s, 2×OMe); 6.54 (2H, s, 2×ArH). ^{13}C NMR ($CDCl_3$): δ 56.52, 57.19, 61.87, 95.02, 110.16, 126.85, 135.90, 150.29, 154.34. HRMS calcd for $C_{16}H_{20}O_6$ 308.1260. Found 308.1259.