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A convenient synthetic approach to dioncoquinone B and related compounds

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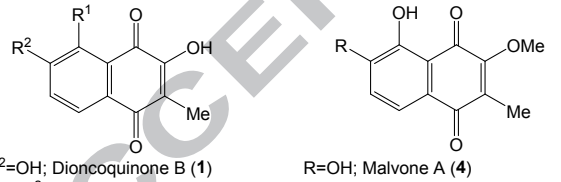
ABSTRACT

A total synthesis of dioncoquinone B and related compounds, including ancistroquinones B, C and malvon A, is presented. The strategy is based on available reagents and can be used as a preparative synthesis of a number of natural and synthetic biologically active (3-alkyl)-2,7,8-di(tri)methoxy(hydroxy)-1,4-naphthoquinones.

1,4-Naphthoquinones comprise an important class of organic compounds that are widely distributed in plants, marine invertebrates, fungi, and bacteria.[1] These compounds attract the attention of researchers due to a wide range of pharmacological properties including antibacterial[2], antiviral[3], trypanocidal[4], anticancer[5], antimalarial[6], and antifungal[7] activity. In particular, dioncoquinone B (**1**) (Figure 1) is of interest due to its promising anti-tumoral and anti-infective activities. It was isolated by Bringmann and coauthors from tropical liana *Triphyophyllum peltatum* and was highly active against *Leishmania major* and multiple myeloma cells without any significant toxicity towards normal blood cells.[8]



R^1=R^2=OH; Dioncoquinone B (**1**)
R^1=OH, R^2=OMe; Ancistroquinone B (**2**)
R^1=R^2=OMe; Ancistroquinone C (**3**)

R=OH; Malvone A (**4**)
R=OMe; 5-Hydroxy-3,6-dimethoxy-2-methyl-1,4-naphthoquinone (**5**) from roots of *Aloe secundiflora*[9]

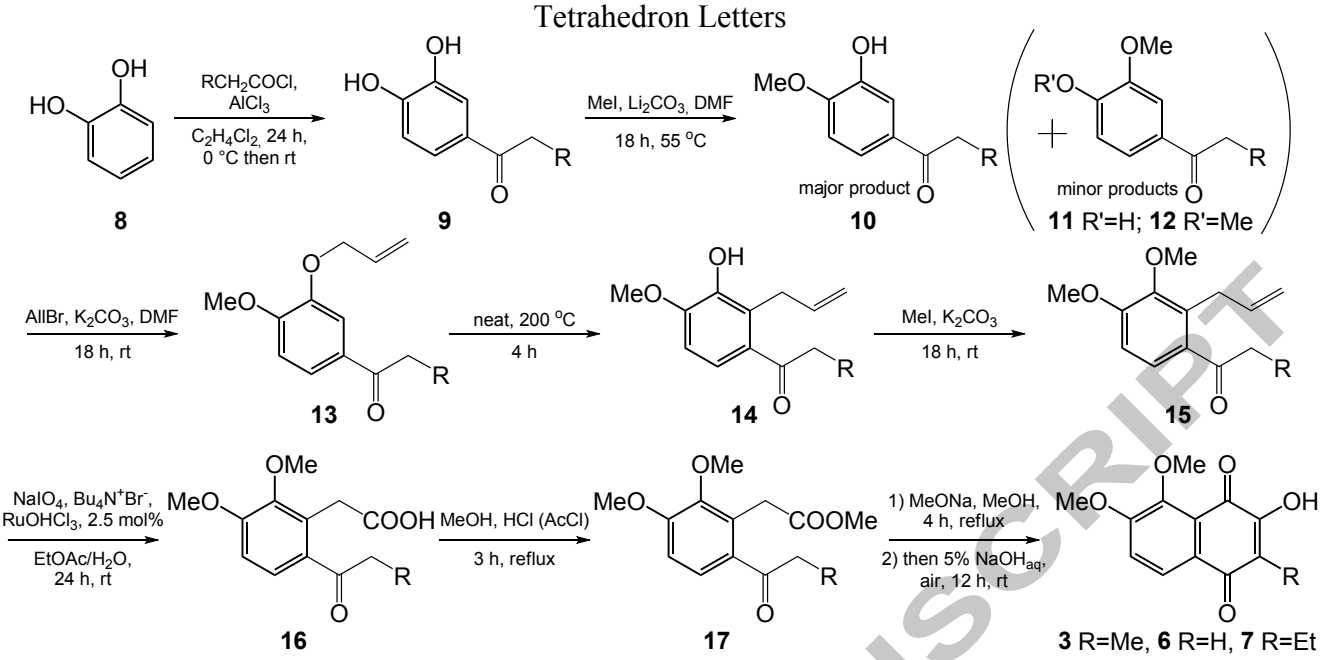
Figure 1. Structures of dioncoquinone B (**1**) and the related naturally occurring compounds.

Bringmann and coauthors also isolated structurally closely related to dioncoquinone B (**1**) naphthoquinones such as ancistroquinones B (**2**), C (**3**), malvone A (**4**), a phytoalexin isolated from *Malva sylvestris* (family Malvaceae),[9] and others from tropical liana *Ancistrocladus abbreviatus*.[8b] Recently, another related naphthoquinone 5-hydroxy-3,6-dimethoxy-2-methyl-1,4-naphthoquinone (**5**), possessing activity against *Mycobacterium tuberculosis* and the Vero cell line, was first isolated from the roots of *Aloe secundiflora* together with other known quinonoid compounds.[10]

It should be noted that naphthoquinones with a similar arrangement of substituents are difficult to access synthetically. So, Bringmann and coauthors reported the first total synthesis of ancistroquinone C (**3**), dioncoquinone B (**1**) and a range of its congeners using three different synthetic approaches including difficult techniques with MeLi, *n*- and *sec*-BuLi at -90 (-78) °C or reduction with LAH. The overall yields of ancistroquinone C (**3**) as a key precursor of dioncoquinone B (**1**) ranged from 19% to 36%.[8b] Malvone A (**4**) was also previously synthesised in 5 steps with an overall yield of 32%, but this synthesis requires the use of unpleasant selenium dioxide and is not suitable for preparative scales.[11] Although, many other regioselective methodologies to access polysubstituted 1,4-naphthoquinone are known.[12]

We needed a straightforward preparative route to access a class of substituted naphthoquinones, because of our interest in synthesis of natural quinonoid compounds and their pharmacologically important derivatives.[13] 2-Hydroxy-1,4-naphthoquinones are of particular interest, since they can be used as starting materials for obtaining a wide range of natural quinonoid compounds and their analogues.[14]

We propose, here, an alternative method for the synthesis of ancistroquinone C (3-hydroxy-2-methyl-5,6-dimethoxy-1,4-naphthoquinone, **3**) and its analogues 2-hydroxy-7,8-dimethoxy-1,4-naphthoquinone (**6**) and 2-ethyl-3-hydroxy-5,6-dimethoxy-1,4-



9-17: R=Me (**a**), H (**b**), Et (**c**)

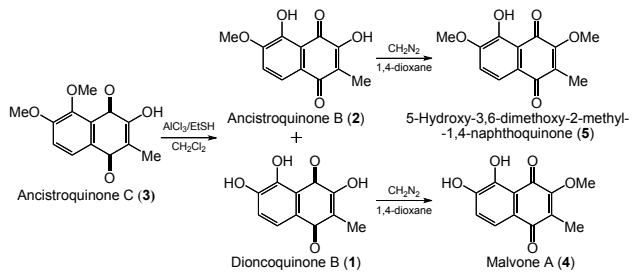
naphthoquinone (**7**) from pyrocatechol with a total yield from 34% to 44%. Despite the multistage nature, this approach mostly uses simple reliable techniques and inexpensive and available reagents.

Scheme 1. Synthesis of ancistroquinone C (**3**) and its analogues **6**,**7**.

The Friedel-Crafts acylation of pyrocatechol (**8**) with propionyl chloride gave 3,4-dihydroxypropiophenone (**9a**)[15] in 88% yield (Scheme 1). The selective methylation of propiophenone **9a** at the 4-position using lithium carbonate as a base gave methoxypropiophenone **10a** in 81% yield[16] however products **11a** and **12a** were also isolated (5% and 3% respectively). The allylation of **10a** gave allyloxymethoxybenzene **13a** (95%), which underwent the Claisen rearrangement to give allylbenzene **14a** in an almost quantitative yield (98%). The methylation of compound **14a** gave allylbenzene **15a** (98%), the oxidation of which produced phenylacetic acid **16a** in the presence of $Ru(OH)Cl_3$ and $NaIO_4$ in 85% yield. The esterification of acid **16a** in absolute methanol in the presence of HCl (AcCl was added) led to the ester **17a** in 98% yield. The Dieckmann cyclization of the ester **17a** and the subsequent oxidation gave ancistroquinone C (**3**) in 82% yield. It should be noted that the conversion of **10a**→**3** (Scheme 1) does not require additional purification of the products and the only stage including chromatographic separation of the product is the conversion of **9a** to **10a**.

A similar sequence of reactions using acetyl chloride or butyryl chloride in the first step gave 2-hydroxy-7,8-dimethoxy-1,4-naphthoquinone (**6**)[17] (overall yield 37%) and 2-ethyl-3-hydroxy-5,6-dimethoxy-1,4-naphthoquinone (**7**) (overall yield 34%) respectively. So this reaction sequence can be used as a general preparative method for obtaining 2-alkyl-3-hydroxy-5,6-dimethoxy-1,4-naphthoquinones.

Ancistroquinone C (**3**) can be used to prepare a number of other naturally occurring quinones.[8b] So, the demethylation of **3** gave dioncoquinone B (**1**) as a major product (75%) while ancistroquinone B (**2**) was also obtained with a yield of 12%. The selective methylation of dioncoquinone B (**1**) and ancistroquinone B (**2**) at the 2-position using diazomethane gave malvone A (**4**) and 5-hydroxy-3,6-dimethoxy-2-methyl-1,4-naphthoquinone (**5**) respectively in an almost quantitative yield (Scheme 2). Synthetic compounds **1-5** were identical in all respects with natural quinones isolated from plants.[8,9,10]



Scheme 2. Synthesis of naturally occurring 1,4-naphthoquinones from ancistroquinone C (**3**).

In summary, the total synthesis of dioncoquinone B (**1**) has been completed in 33% overall yield with a linear sequence of 9 steps. The synthetic pathway developed allows convenient access to various naturally occurring (3-alkyl)-2,7,8-di(tri)methoxy(hydroxy)-1,4-naphthoquinones on preparative scales and does not require complex techniques and expensive reagents. It is envisaged that the strategy described will allow access to other members of the 2-alkyl-3-hydroxy-5,6-dimethoxy-1,4-naphthoquinones family that have eluded synthetic efforts and make these compounds more accessible for further synthetic modification and their biological activity study.

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Supplementary Material

General experimental procedures, Mass and NMR spectral data for compounds are provided in supporting information.

Highlights:

- Gram-scale synthesis
- Available inexpensive reagents
- Simple techniques

Graphical Abstract

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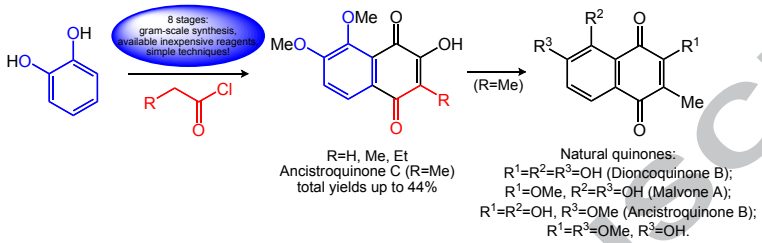

R=H, Me, Et
Ancistroquinone C (R=Me)
total yields up to 44%

Natural quinones:
R^1=R^2=R^3=OH (Dioncoquinone B);
R^1=OMe, R^2=R^3=OH (Malvone A);
R^1=R^2=OH, R^3=OMe (Ancistroquinone B);
R^1=R^3=OMe, R^3=OH.