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Synthesis of a Dimeric Pyranonaphthoquinone *via* a Novel Double Furofuran Annulation Strategy

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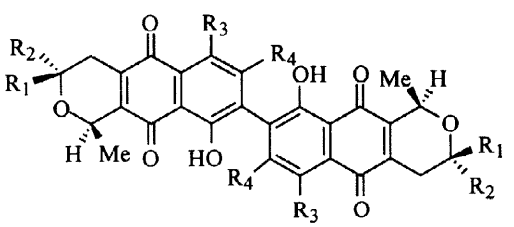
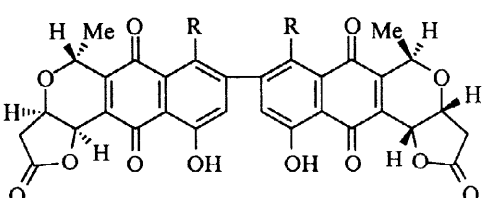
Abstract: The first synthesis of a dimeric pyranonaphthoquinone **16** which is related to the naturally occurring dimeric pyranonaphthoquinones, e.g. actinorhodin **1** and crisamycin **3**, is described. The key biaryl **8** is prepared by means of a Suzuki coupling reaction, utilizing the Miyaura reagent to generate the organoboron coupling partner. The first example of a double annulation of a bisquinone with 2-trimethylsilyloxyfuran to afford a bisfuronaphthofuran and subsequent double oxidative rearrangement to a dimeric pyranonaphthoquinone is described.

The monomeric pyranonaphthoquinones, e.g. arizonin[1] and kalafungin,[2] have attracted considerable synthetic interest,[3] partly due to Moore's proposal that they act as bioreductive alkylating agents.[4] Our synthetic approach to the monomeric pyranonaphthoquinones involved a furofuran annulation and subsequent oxidative rearrangement to a pyranonaphthoquinone.[5] Dimeric pyranonaphthoquinones, e.g. actinorhodins **1**, **2**, the antiviral crisamycin A **3**[6] and the antileukemic cardinalins e.g. **4**[7] also occur naturally. In contrast to the monomeric pyranonaphthoquinones no total synthesis of a dimeric pyranonaphthoquinone has been reported. A partial synthesis of actinorhodin **1** starting from a degradation product of the antibacterial metabolite α-naphthocyclinone has been reported by Laatsch.[8] Herein we report the first synthesis of a dimeric pyranonaphthoquinone system which lays the foundation for the synthesis of other naturally occurring dimeric pyranonaphthoquinones.



R_1=R_4=H; R_2=CH_2CO_2H; R_3=OH: Actinorhodin **1**
R_1=Me; R_2=R_3=H; R_4=OMe: Cardinalin 3 **4**



R=OH: γ-Actinorhodin **2**
R=H: Crisamycin A **3**

Our approach to dimer **16** (Scheme 2) hinged on the double furofuran annulation of bisquinone **9** (Scheme 2) with 2-trimethylsilyloxyfuran to form bisadduct **10**. Double oxidative rearrangement of

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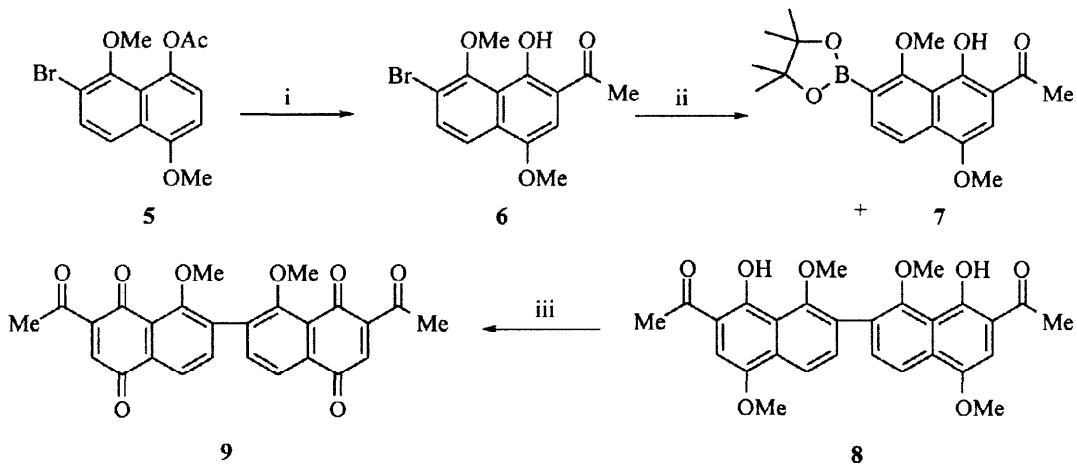
furonaphthofuran **10** then provides the desired dimeric pyranonaphthoquinone skeleton. Construction of bisquinone **9** from acetate **5**[9] was therefore the initial synthetic objective.

Fries rearrangement of acetate **5** afforded 2-acetyl naphthol **6**[9] (Scheme 1) which underwent "*in situ*" formation of the isolable pinacol boronate **7**,[10] in the presence of the Miyaura reagent diboron pinacolate[11] and $PdCl_2(dppf)$.[12] Subsequent "one-pot" Suzuki coupling[13] with unreacted bromonaphthalene **6** afforded biaryl **8** along with unreacted **7** which was then recycled. The use of the Miyaura reagent was essential for successful biaryl formation due to the presence of the *o*-hydroxy ketone functionality which is incompatible with the traditional routes to boronic acids.[11] This approach proved superior to earlier attempts to prepare bis-naphthalene **8** using a double Fries rearrangement. Biaryl **8** was then converted to the desired bisnaphtho-quinone **9** using ceric ammonium nitrate (CAN) as the oxidant.



Reagents and Conditions: (i) $BF_3.OEt_2$, 120°C, 71%; (ii) $PdCl_2(dppf)$, CsF (4 equiv.), diboron pinacolate (4 equiv.), THF, reflux, 25h., **7**:19%, **8**:53%; (iii) CAN (4 equiv.), $CH_3CN_{(aq)}$, 72%.

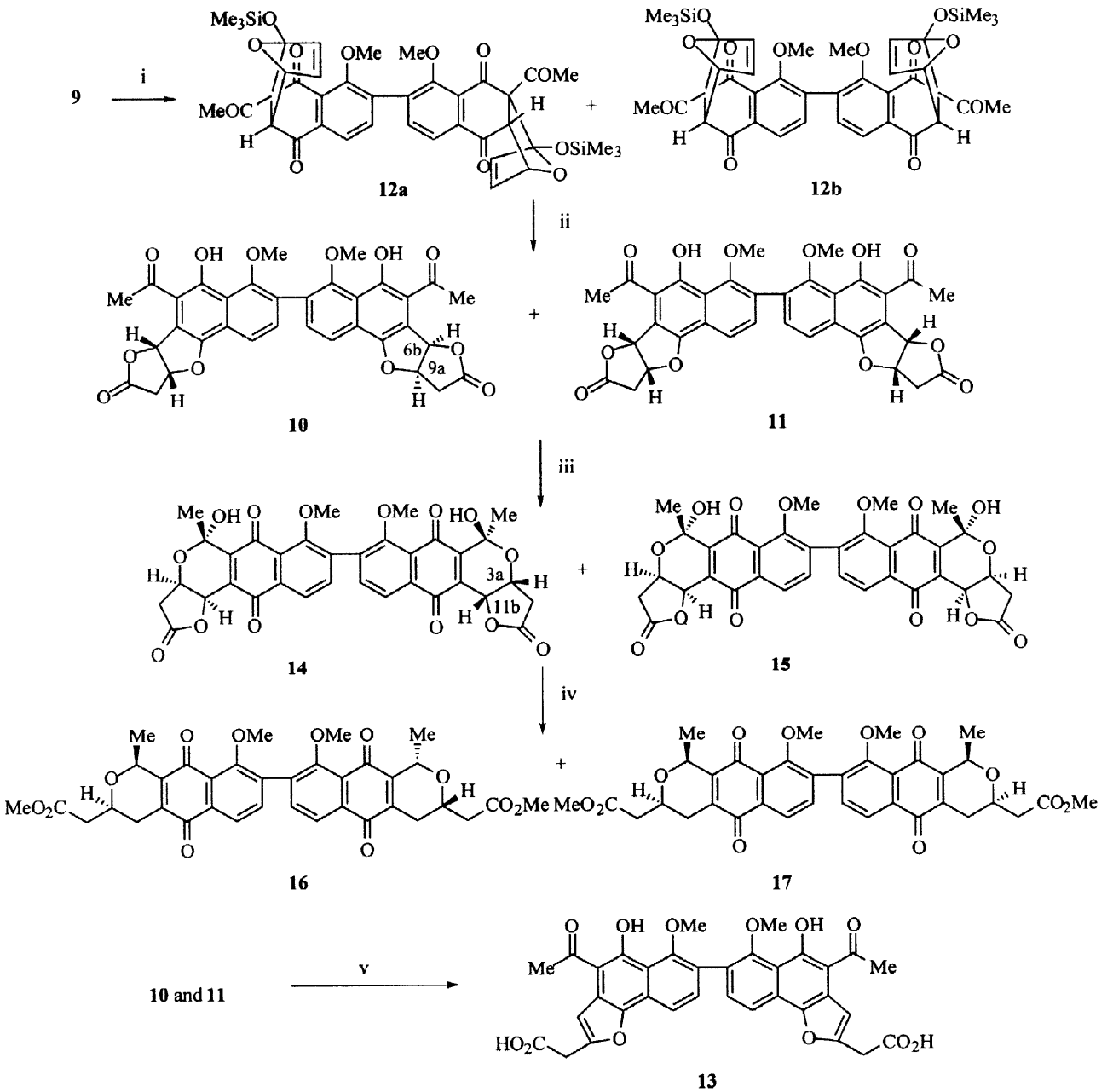
Scheme **1**

The first example of a double annulation of a bisquinone with 2-trimethylsilyloxyfuran was then effected, affording a 1:1 inseparable mixture of adducts **10** and **11** after purification on silica gel (Scheme 2). Notably the ^1H nmr of the crude reaction mixture supported initial formation of a Diels-Alder adduct, tentatively assigned as bis-*endo* adducts **12a/b**. The chemical shifts of the bridgehead and vinylic protons in **12** were in excellent agreement with analogous protons reported in the literature.[14] Diels-Alder adducts **12a/b** then underwent fragmentation to the diastereomeric furo[3,2-b]naphtho[2,1-d]furans **10** and **11** upon purification on flash silica. The ^1H nmr spectrum of the dimer was in excellent agreement with the monomeric system.[5a] Adducts **10** and **11** proved to be very unstable and underwent ring opening of the γ-lactone rings affording biscarboxylic acid **13** upon standing in chloroform.

Double oxidative rearrangement of furonaphthofurans **10** and **11**, using CAN in aqueous acetonitrile,[5,15] afforded an inseparable mixture of hemiacetals **14** and **15**. The ^1H nmr of the hemiacetals was in excellent agreement with that reported for the monomeric system[5a] and the stereochemistry was assigned by analogy to the monomeric system.[5a] Hydrogenation of the hemiacetals **14** and **15** in ethyl acetate over palladium on charcoal resulted in reduction of the hemiacetal group to a cyclic ether together with hydrogenolysis of the γ-lactone.[16] Treatment of the resultant carboxylic acid with an ethereal solution of diazomethane facilitated purification by flash chromatography affording a 1:1 mixture of bis-methyl esters **16** and **17**, which are closely

related to the bis-methyl ester of actinorhodin **1**. The stereochemistry of bis-methyl esters **16** and **17** was also assigned by analogy to the monomeric system.[5a]

In conclusion we have achieved the first synthesis of a dimeric pyranonaphthoquinone employing a double annulation/oxidative rearrangement strategy. The methodology developed in the present work should allow access to more elaborate pyranonaphthoquinone dimers *e.g.* crisamycin A **3** and cardinalin 3 **4**.



Reagents and Conditions: (i) 2-trimethylsilyloxyfuran, CH_3CN, 0°C, 1h.; (ii) Silica gel, EtOAc-hexane (2:1), 52%; (iii) CAN (4 equiv.), $CH_3CN_{(aq)}$, 0°C, 0.25h., 55%; (iv) 10% Pd/C, $H_{2(g)}$, EtOAC, 2h, then excess CH_2N_2, Et_2O, 78%; (v) $CHCl_3$, H^+(trace), 0.25h., r.t., 100%.

Scheme **2**

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[17] Selected data for adducts **10** and **11**; yellow oil; [Found (CI): $M^{+}H$ 627.14810. $C_{34}H_{27}O_{12}$ requires $M^{+}H$, 627.15023]; υ_{max}(film) 3243 (OH), 1782 (C=O, γ-lactone) and 1625 cm^{-1} (C=O, *o*-hydroxyaryl ketone); δ_H[400 MHz; $CDCl_3$] 2.83 (6H, s, CH_3), 3.06 (2H, dd, J_{gem} 19.1 and $J_{9,9a}$ 2.4, 9-H), 3.12 (2H, dd, J_{gem} 19.1 and $J_{9',9a}$ 5.7, 9-H'), 3.62 (6H, s, OCH_3), 5.47 (2H, ddd, $J_{9a,9'}$ 5.7, $J_{9a,6b}$ 5.7 and $J_{9a,9}$ 2.4, 9a-H), 6.52 (2H, d, $J_{6b,9a}$ 5.7, 6b-H), 7.71 (2H, d, $J_{1,2}$ 8.5, ArH) and 7.77 (2H, d, $J_{2,1}$ 8.5, ArH); δ_C[100.6 MHz; $CDCl_3$] 32.3 (CH_3, $COCH_3$), 36.3 (CH_2, C-9), 63.1 (OCH_3), 81.8 (CH, C-9a), 86.3 (CH, C-6b), 113.9, 114.8, 121.6, 126.4, 130.5 (quat., C-3, C-4a, C-6, C-6a, C-10b), 119.4 (CH, C-1), 134.0 (CH, C-2), 150.9, 156.9, 158.3 (quat., C-4, C-5, C-10a), 175.0 (quat., C-8) and 202.2 (quat., $COCH_3$).

Data for adducts **14** and **15**; yellow oil; [Found (EI): $M^{+}H$, 659.13536. $C_{34}H_{26}O_{14}$ requires $M^{+}H$, 659.14006]; υ_{max}(film) 3443 (OH), 1783 (C=O, γ-lactone) and 1666 cm^{-1} (C=O, quinone); δ_H[400 MHz; $(CD_3)_2CO$] 1.83 (6H, s, CH_3), 1.84* (6H, s, CH_3), 2.51 (2H, d, J_{gem} 17.6, 3-H), 3.20 (2H, dd, J_{gem} 17.6 and $J_{3',3a}$ 5.2, 3-H'), 3.67 (6H, s, OCH_3), 5.00 (2H, dd, $J_{3a,3'}$ 5.2, $J_{3a,11b}$ 3.2, 3a-H), 5.40 (2H, d, $J_{11b,3a}$ 3.2, 11b-H), 5.90 (2H, brs, OH), 7.81 (2H, d, $J_{10,9}$ 8.0, H-10), 7.82* (2H, d, $J_{10,9}$ 8.0, H-10), 7.97 (2H, d, $J_{9,10}$ 8.0 H-9) and 7.98* (2H, d, $J_{9,10}$ 8.0, H-9); δ_C[100.6 MHz; $(CD_3)_2CO$] 26.8 (CH_3), 36.8 (CH_2, C-3), 62.3 (OCH_3), 67.2 (CH, C-3a), 69.7 (CH, C-11b), 93.8 (quat., C-5), 122.0 (CH, C-10), 122.1 (quat., C-8), 125.9, 134.4, 139.8, 148.4 (quat., C-5a, C-6a, C-10a, C-11a), 136.7 (CH, C-9), 158.7 (quat., C-7), 175.2 (quat., C-2) and 183.2, 183.5 (quat., C-6, C-11). *Denotes resonance for diastereomer.