A Facile Enantioselective Synthesis of the Dimeric Pyranonaphthoquinone Core of the Cardinalins

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Abstract: The enantioselective synthesis of a dimeric pyranonaphthoquinone closely related to cardinalin 3 is described. Key steps include the Hauser–Kraus annulation between a cyanophthalide and a chiral enone to create the naphthalene skeleton, a Suzuki–Miyaura homocoupling of an aryl triflate to construct the biaryl bond and a double stereoselective lactol reduction to install the 1,3-*cis* stereochemistry of the pyran rings.

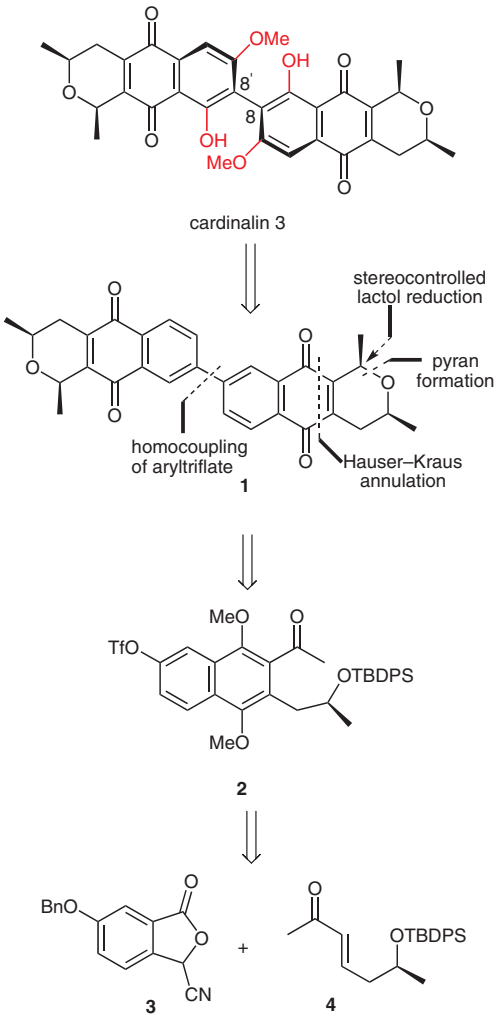
Key words: cardinalin, pyranonaphthoquinone antibiotics, Hauser–Kraus annulation, homocoupling

The pyranonaphthoquinone family of antibiotics exhibits activity against a variety of Gram-positive bacteria, pathogenic fungi and yeasts[1] and they have been proposed to act as bioreductive alkylating agents.[2] Whilst the synthesis of monomeric members of this important family of antibiotics is well documented,[1b,c] the enantioselective total synthesis of a dimeric pyranonaphthoquinone antibiotic has yet to be achieved.[1,3]

The cardinalins are a series of biologically active dimeric pyranonaphthoquinone pigments isolated from the New Zealand toadstool *Dermocybe cardinalis*[4] that have aroused considerable interest in our laboratory. The simplest member of the family, cardinalin 3 possesses two *cis*-1,3-dimethylpyran rings that are fused to their respective naphthoquinone nuclei that in turn are linked via a C8–C8′ biaryl bond and exists as a single atropisomer (Scheme 1). Our long-standing interest in the synthesis of pyranonaphthoquinones[1b,c] combined with the challenging dimeric structure and biological activity of the cardinalins prompted us to instigate a synthetic program towards their synthesis.

In light of the fact that no enantioselective synthesis of a dimeric pyranonaphthoquinone currently exists in the literature, it was decided to focus initially on the asymmetric synthesis of the biaryl core of cardinalin 3, namely model dimeric pyranonaphthoquinone **1** (Scheme 1). This work follows on from several syntheses of dimeric pyranonaphthoquinones where the issue of enantioselectivity was not addressed.[1,3]

The retrosynthesis is based on our own methodology for the stereoselective construction of *cis*-1,3-dimethylpyran rings which has recently been implemented in an enantioselective total synthesis of the topoisomerase II inhibitor eleutherin.[5] Thus in the present work, model dimer **1** was envisaged to be accessible via a double stereoselective reduction[6] of a bislactol that in turn would be accessible by double intramolecular pyran ring formation. The naphthoquinone core can be formed using a Hauser–Kraus annulation[7,8] and a late stage Suzuki–Miyaura homocoupling of a suitable aryl triflate to form the key biaryl bond.



Scheme 1 Retrosynthetic analysis of model dimer **1**

During our preliminary synthetic efforts towards the related dimeric pyranonaphthoquinone crisamicin A, we encountered limited success using a double Hauser–Kraus annulation with a biscyanophthalide as a means to access

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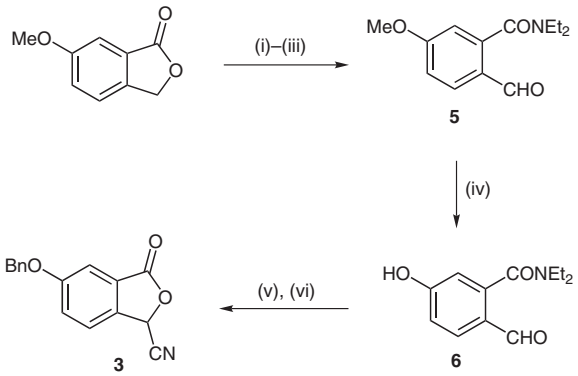
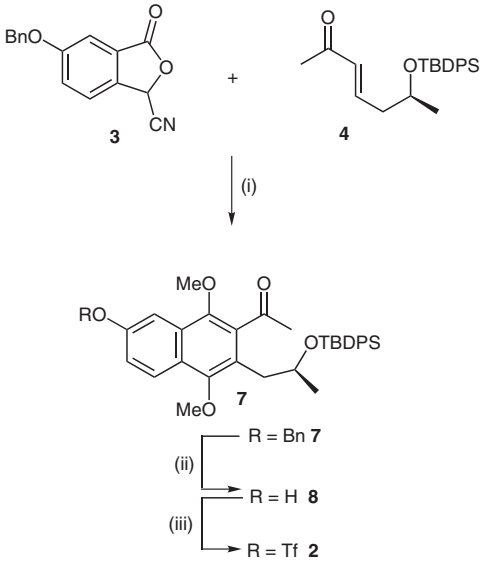
the biaryl core.[9] Our revised strategy reported herein focuses on conducting the key homocoupling step to forge the biaryl unit at an advanced stage of the synthesis. Towards this end, Hauser–Kraus annulation of a suitably protected cyanophthalide with an enone coupling partner was envisaged as a crucial step to construct an appropriately functionalized monomeric naphthalene ring. Given that chiral enone **4** was in hand,[5] attention turned to the synthesis of the benzyl-protected cyanophthalide **3** that upon annulation with enone **4** could be easily converted into an aryl triflate substrate ready for the proposed late-stage homocoupling.

Thus, by simple modification of a literature procedure,[10] 6-methoxyphthalide[11] was subjected to radical ring opening with *N*-bromosuccinimide. The resulting crude acid thus obtained was then converted into its diethylamide via the acid chloride furnishing amide **5**.[12] The methyl ether surprisingly resisted all attempts to effect its cleavage with conventional Lewis acids (BBr_3, BCl_3, $AlCl_3$), leading to degradation and only trace amounts of product being isolated. Fortunately, the use of thiophenol in the presence of catalytic quantities of potassium carbonate at elevated temperature in *N*-methylpyrrolidinone[13] successfully furnished phenol **6** in good yield. Smooth benzylation followed by ring closure by using trimethylsilyl cyanide in the presence of catalytic quantities of potassium cyanide and 18-crown-6[14] delivered the cyanophthalide annulation precursor **3** (Scheme 2).



Scheme 2 *Reagents and conditions*: (i) NBS, CCl_4–PhH, reflux, 6 h then H_2O, 90 °C, 2 h; (ii) $SOCl_2$, 70 °C, 2 h; (iii) $HNEt_2$, CH_2Cl_2, 0 °C to r.t., 2 h, 42% (3 steps); (iv) PhSH, K_2CO_3, NMP, 130 °C, 2 h, 77%; (v) BnBr, K_2CO_3, acetone, r.t., 16 h; (vi) TMSCN, 18-crown-6, KCN, CH_2Cl_2, 0 °C to r.t., 2 h then AcOH, r.t., 16 h, 90% (2 steps).

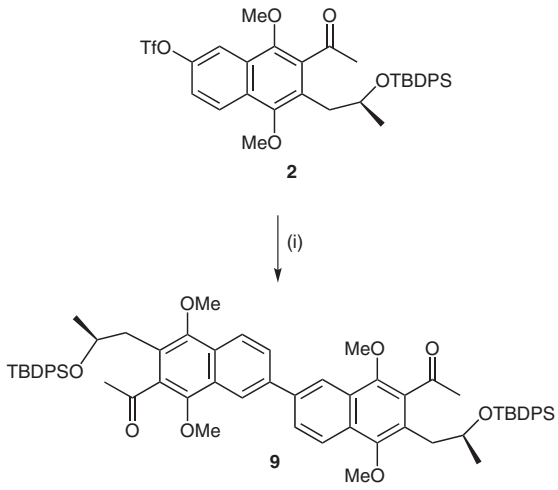
With cyanophthalide **3** in hand, the stage was now set for the key Hauser–Kraus annulation. Thus, reaction of cyanophthalide **3** with enone **4** proceeded smoothly in the presence of potassium *tert*-butoxide in DMSO. Immediate reductive methylation of the crude annulation product with potassium carbonate and dimethylsulfate under phase-transfer conditions was necessary to facilitate isolation of the product **7**. Facile debenzylation delivered phenol **8** that underwent smooth triflate formation using *N*-trifluoromethanesulfonimide in the presence of DMAP and triethylamine furnishing the key aryl triflate homocoupling precursor **2** in excellent overall yield (Scheme 3).



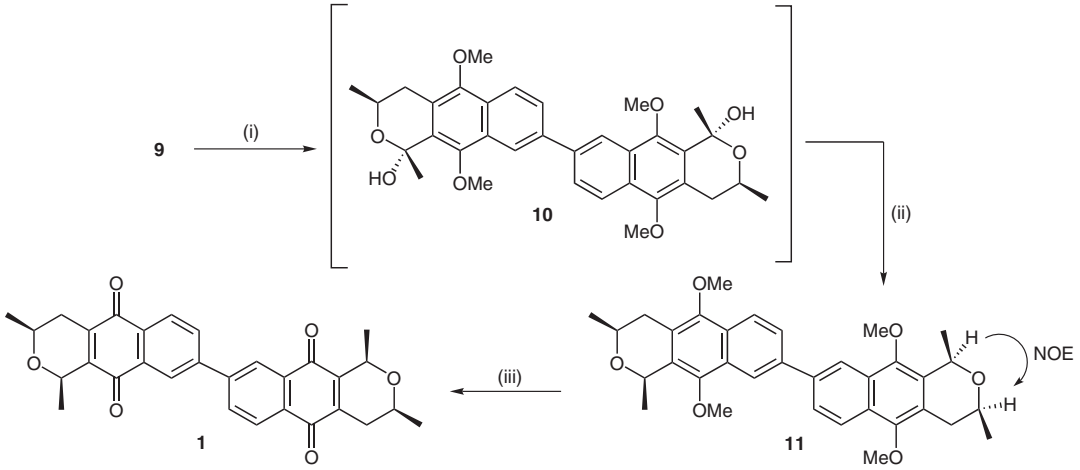
Scheme 3 *Reagents and conditions*: (i) KO*t*-Bu, DMSO, r.t., 30 min then Me_2SO_4, K_2CO_3, Me_2SO_4, TBAI, $Na_2S_2O_4$, THF–H_2O, r.t., 2 h, 87%; (ii) H_2, Pd/C, MeOH, r.t., 18 h, 97%; (iii) $PhN(OTf)_2$, DMAP, Et_3N, CH_2Cl_2, r.t., 1 h, 95%.

Next, the key Suzuki–Miyaura homocoupling step was undertaken. After careful optimization, it was found that microwave irradiation (300 W, 150 °C) of a dioxane solution of triflate **2** with precisely 0.5 equivalents of bis(pinacolato)diboron, three equivalents of freshly ground dried potassium carbonate under $Cl_2Pd(dppf)$–dppf catalysis (10 mol%) for one hour gratifyingly afforded the homocoupled product **9**[15] in 51% yield in a one-pot operation (Scheme 4).

With a synthetic route to biaryl **9** successfully established, the double pyran ring formation could next be attempted. Treatment of biaryl **9** with an excess of tetrabutylammonium fluoride in tetrahydrofuran effected removal of both



Scheme 4 *Reagents and conditions*: (i) $Cl_2Pd(dppf)$ (10 mol%), dppf, K_2CO_3, bis(pinacolato)diboron, dioxane, microwave, 150 °C, 1 h, 51%.



Scheme 5 *Reagents and conditions*: (i) TBAF, THF, r.t., 72 h (ii) TFA, CH_2Cl_2, –78 °C, 30 min then Et_3SiH, r.t., 16 h, 70% (2 steps); (iii) CAN, MeCN–H_2O, r.t., 45 min, 63%.

tert-butyldiphenylsilyl ether protecting groups with concomitant in situ cyclization. Due to the unstable nature of bislactol **10** it was immediately reduced to the bis-*cis*-1,3-dimethylpyran **11**[16] with trifluoroacetic acid and triethylsilane following the procedure described by Kraus.[6] The formation of a single product was observed by ^{1}H NMR indicating the formation of the all *cis*-diastereomer resulting from pseudo-axial delivery of the hydride during the reduction step.[6]

The 1,3-*cis* stereochemistry was confirmed unequivocally by the NOE correlation between the axial protons at C1 and C3 on the pyran ring. Finally, CAN-mediated oxidative demethylation provided the bisquinone 7,7′-demethoxy-9,9′-deoxycardinalin 3 (**1**,[17] Scheme 5).

In conclusion, we have achieved an efficient synthesis of the dimeric core structure of cardinalin 3, representing the first enantioselective synthesis of a dimeric pyranonaphthoquinone. The combined use of a Hauser–Kraus annulation followed by a Suzuki–Miyaura homocoupling provides a flexible synthetic strategy for the synthesis of the cardinalins and related dimeric pyranonaphthoquinones. Work towards this end is in progress.

Acknowledgment

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(15) Compound **9**: colorless oil; $[\alpha]_D^{25}$ –21.8 (c 2.5, CH_2Cl_2); IR (oil): ν_{max} = 3070, 3049, 2959, 2932, 2894, 1679, 1588, 1450, 1427, 1348, 1330, 1204, 1112 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 0.97 [18 H, s, 2 × $C(CH_3)_3$], 0.98 (6 H, d, $^3J_{HH}$ = 6.0 Hz, 2 × CH_3), 2.48 (6 H, s, 2 × $C{=}OCH_3$), 2.90 (2 H, dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 7.5 Hz, 2 × C*H*H), 3.11 (2 H, dd, $^2J_{HH}$ = 13.4 Hz, $^3J_{HH}$ = 6.7 Hz, 2 × CH*H*), 3.81 (6 H, s, 2 × OCH_3), 3.90 (6 H, s, 2 × OCH_3), 4.27 [2 H, ddq (app. sext), $^3J_{HH}$ = 7.5, 6.7, 6.0 Hz, 2 × CH], 7.27 (4 H, m, ArH), 7.38 (8 H, m, ArH), 7.54 (4 H, dd, *J* = 8.1, 1.3 Hz, ArH), 7.66 (4 H, dd, *J* = 8.1, 1.6 Hz, ArH), 7.93 (2 H, dd, *J* = 8.8, 1.8 Hz, ArH), 8.15 (2 H, d, *J* = 8.8 Hz, ArH), 8.36 (2 H, d, *J* =

1.8 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.1 {2 × Si[*C*(CH_3)$_3$]}, 23.4 (2 × CH*C*H_3), 27.0 {2 × Si[C(*C*H_3)$_3$]}, 32.8 (2 × C=O*C*H_3), 37.0 (2 × CH_2), 61.8 (2 × OCH_3), 63.7 (2 × OCH_3), 69.6 (2 × CH), 120.6 (2 × CH_{arom}), 123.7 (2 × CH_{arom}), 124.8 (2 × C_{arom}), 126.8 (2 × CH_{arom}), 127.4 (8 × CH_{arom}), 127.9 (2 × C_{arom}), 128.3 (2 × C_{arom}), 129.40 (2 × CH_{arom}), 129.43 (2 × CH_{arom}), 134.27 (2 × C_{arom}), 134.31 (2 × C_{arom}), 134.7 (2 × C_{arom}), 135.8 (4 × CH_{arom}), 135.9 (4 × CH_{arom}), 138.6 (2 × C_{arom}), 149.3 (2 × C_{arom}), 151.6 (2 × C_{arom}), 205.3 (2 × C=O). MS–FAB: *m/z* (%) = 1050 (4) $[M]^+$, 993 (6) $[M - C(CH_3)_3]^+$, 795 (14), 397 (10), 197 (40), 135 (100). HRMS–FAB: *m/z* calcd for $C_{66}H_{74}O_8Si_2$ $[M]^+$: 1050.4922; found: 1050.4921.

(16) Compound **11**: cream-colored solid; mp 268–269 °C; $[\alpha]_D^{24}$ +36.2 (*c* 0.12, CH_2Cl_2). IR (CH_2Cl_2): ν_{max} = 3418, 3053, 2986, 1638, 1421, 1264, 733 cm^{-1}. ^{1}H NMR (300 MHz, $CDCl_3$): δ = 1.44 (6 H, d, $^3J_{HH}$ = 6.0 Hz, 2 × CHCH_3), 1.73 (6 H, d, $^3J_{HH}$ = 6.6 Hz, 2 × CHCH_3), 2.66 (2 H, dd, $^2J_{HH}$ = 16.2 Hz, $^3J_{HH}$ = 11.0 Hz, 2 × C*H*H), 3.11 (2 H, dd, $^2J_{HH}$ = 16.2 Hz, $^3J_{HH}$ = 1.5 Hz, 2 × CH*H*), 3.74 (2 H, m, 2 × C*H*CH_3), 3.91 (6 H, s, 2 × OCH_3), 3.95 (6 H, s, 2 × OCH_3), 5.26 (2 H, q, $^3J_{HH}$ = 6.6 Hz, 2 × C*H*CH_3), 7.89 (2 H, dd, $^3J_{HH}$ = 8.8 Hz, $^4J_{HH}$ = 1.6 Hz, ArH), 8.18 (2 H, d, $^3J_{HH}$ = 8.8 Hz, ArH), 8.37 (2 H, d, $^4J_{HH}$ = 1.6 Hz, ArH). ^{13}C NMR (75 MHz, $CDCl_3$): δ = 21.8 (2 × CH*C*H_3), 22.4 (2 × CH*C*H_3), 32.0 (2 × CH_2), 61.1 (2 × OCH_3), 61.4 (2 × OCH_3), 69.6 (2 × CH), 71.3 (2 × CH), 120.4 (2 × CH_{arom}), 122.8 (2 × CH_{arom}), 125.5 (2 × C_{arom}), 125.7 (2 × CH_{arom}), 126.6 (2 × C_{arom}), 127.7 (2 × C_{arom}), 129.9 (2 × C_{arom}), 138.3 (2 × C_{arom}), 148.8 (2 × C_{arom}), 149.0 (2 × C_{arom}). MS (EI): *m/z* (%) = 542 (100) $[M]^+$, 527 (39), 199 (22), 105 (32), 57 (40), 44 (72). HRMS (EI): *m/z* calcd for $C_{34}H_{38}O_6$ $[M]^+$: 542.2668; found: 542.2667.

(17) Compound **1**: yellow solid; mp 239–240 °C; $[\alpha]_D^{23}$ +356.1 (*c* 0.15, CH_2Cl_2). IR (CH_2Cl_2): ν_{max} = 3432, 3025, 1663, 1265, 736, 705 cm^{-1}. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.40 (6 H, d, $^3J_{HH}$ = 6.1 Hz, 2 × CHCH_3), 1.58 (6 H, d, $^3J_{HH}$ = 6.5 Hz, 2 × CHCH_3), 2.31 (2 H, ddd, J_{HH} = 18.7, 10.2, 4.0 Hz, 2 × CH_{ax}H), 2.82 (2 H, dt, J_{HH} = 18.7, 2.5 Hz, 2 × CH_{eq}H), 3.64 (2 H, m, 2 × C*H*CH_3), 4.89 (2 H, m, 2 × C*H*CH_3), 8.02 (2 H, dd, $^3J_{HH}$ = 8.0 Hz, $^4J_{HH}$ = 1.9 Hz, ArH), 8.20 (2 H, d, $^3J_{HH}$ = 8.0, ArH), 8.35 (2 H, $^4J_{HH}$ = 1.9 Hz, ArH). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8 (2 × CH*C*H_3), 21.2 (2 × CH*C*H_3), 30.5 (2 × CH_2), 68.7 (2 × CH), 70.0 (2 × CH), 125.0 (2 × CH_{arom}), 127.3 (2 × CH_{arom}), 131.4 (2 × CH_{arom}), 131.9 (2 × C_{arom}), 133.0 (2 × C_{arom}), 143.0 (2 × C_{arom}), 144.2 (2 × C_{arom}), 147.0 (2 × C_{arom}), 183.4 (2 × C=O), 183.7 (2 × C=O). MS (EI): *m/z* (%) = 482 (100) $[M]^+$, 467 (20), 237 (15), 199 (20), 131 (21), 91 (99), 77 (25), 57 (37), 40 (85). HRMS (EI): *m/z* calcd for $C_{30}H_{26}O_6$ $[M]^+$: 482.1729; found: 482.1720.