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Synthesis and absolute configuration of cordiaquinone K, antifungal and larvicidal meroterpenoid isolated from the Panamanian plant, *Cordia curassavica*

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Abstract—Total synthesis of cordiaquinone K, a new antifungal and larvicidal meroterpenoid, is reported. The absolute configuration of cordiaquinone K was confirmed by the synthesis. © 2003 Elsevier Ltd. All rights reserved.

Cordiaquinones are antifungal and larvicidal meroterpenoids isolated from Panamanian plants such as *Cordia linnaei*. In 1990, Messana and co-workers reported the isolation and structures of cordiaquinones A (1) and B (2) (Fig. 1).¹ After their identification of cordiaquinones from the plant, several cordiaquinones have been isolated.^{2,3} In 2000, Hostettmann and coworkers reported the structures of cordiaquinones J (3) and K (4) isolated from *C. curassavica* (Fig. 1).⁴ These compounds exhibit antifungal activities against phytopathogenic fungus such as *Cladosporium cucumerinum* and larvicidal activity against the larvae of the yellow fever-transmitting mosquito *Aedes aegypti*. The structures of cordiaquinone J and K were established on the basis of HRMS, UV and 1D and 2D NMR spectra. The synthesis and absolute configuration of cordiaquinone B were reported by Asaoka and his coworkers.⁵ The absolute stereochemistry of other cordiaquinones, however, remained unknown. In connection with our synthetic studies of biologically active natural terpenoids,⁶ we became interested in clarifying the absolute configuration of cordiaquinones. This communication describes the total synthesis of (+)-cordiaquinone K employing one-pot B-alkyl Suzuki-Miyaura coupling⁷ as a key step and the determination of the absolute configuration of the natural product.



Figure 1. Structures of cordiaquinones.

Keywords: synthesis; B-alkyl Suzuki–Miyaura coupling; cordiaquinones; absolute configuration. * Corresponding author. Fax: +81-3-5477-2622; e-mail: yabta@nodai.ac.jp

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As our target, we first chose (\pm) -13-deoxocordiaquinone K (5), since there was an urgent need to establish the appropriate conditions of the coupling reaction. Scheme 1 summarizes our synthesis of (\pm) -13-deoxocordiaquinone K (5). 6-Bromonaphtoquinone⁸ (6) and (\pm) - γ -cyclohomogeraniol⁹ (8) were selected as the starting materials. 6-Bromonaphtoquinone (6) was first hydrogenated with PtO₂ followed by methylation of the resulting hydroxyl groups to give 7.¹⁰ (\pm)- γ -Cyclohomogeraniol (8) was converted to known iodide (9).^{6a,11} To connect the γ -cyclohomogeranyl unit (9) and the naphtoquinone derivative (7), we examined one-pot B-alkyl Suzuki-Miyaura coupling reaction. This protocol would be useful for the syntheses of terpenoids such as ambrein,¹² luffarin W,¹³ penlanpallescensin,¹⁴ etc. (Fig. 2), because these compounds have a common structural feature with cordiaquinone K, namely a ycyclohomogeranyl unit connecting with an aryl or a vinyl unit.

As a preliminary experiment for the coupling of 9 with 7, the conditions reported by Marshall and Johns^{15,16} {PdCl₂(dppf) as a catalyst} were examined to give the desired product (10) in only 10% yield based on 9. Then we examined various conditions. Table 1 summarizes reaction conditions and yields of 10. Although PdCl₂(dppf) was not an effective catalyst (entries 1-3), $Pd(PPh_3)_4$ was superior in yield (entry 4). Moreover, by heating the reaction mixture to 80°C, 50% yield of 10 was obtained (entry 6). This indicates that the yield based on 7 was quantitative. Increasing the stoichiometry of 7, however, showed only a slight improvement (55%, entry 7). Other palladium catalysts such as $Pd_2(dba)_3$, $PdCl_2(dppe)$, $PdCl_2(dppp)$, $Pd(PEt_3)_2Cl_2$, $Pd(OAc)_2+2Cy_3P$ and allylpalladium chloride dimer or a combination of bases such as Ba(OH)₂, TlOEt and Cs₂CO₃ were also examined, but we found $Pd(PPh_3)_4$ with K_3PO_4 is the best choice for the coupling reaction.



Scheme 1. Synthesis of (\pm) -13-deoxocordiaquinone K. *Reagents, conditions and yields.* (a) (1) H₂, PtO₂, EtOAc; (2) NaH, MeI, DMF (89%, two steps); (b) Ref. 6a (92%, two steps); (c) (1) 2 equiv. *t*-BuLi, ether, -78° C; (2) 2.5 equiv. B-MeO-9-BBN, hexane, THF; (3) 2.5 equiv. base; (4) 5 mol% Pd catalyst, 7, DMF (see Table 1); (d) CAN, CH₃CN, 0°C (73%).



Figure 2. Structures of natural products with related structure of cordiaquinones.

Table	1.	Reaction	conditions	and	yields	of	1(J
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Entry	Pd catalyst ^a	Equiv. of 7	Temp. (°C)	Base ^b	Time (h)	Yield (%) ^c
1	PdCl ₂ (dppf)	0.5	Rt	K ₃ PO ₄	16	10
2	PdCl ₂ (dppf)	0.5	Rt	K ₃ PO ₄	120	13
3	PdCl ₂ (dppf)	0.5	80	K ₃ PO ₄	16	12
4	$Pd(PPh_3)_4$	0.5	Rt	K ₃ PO ₄	16	24
5	$Pd(PPh_3)_4$	0.5	Rt	K ₃ PO ₄	72	22
6	$Pd(PPh_3)_4$	0.5	80	K ₃ PO ₄	16	50
7	$Pd(PPh_3)_4$	1	80	K ₃ PO ₄	16	55
8	$Pd(PPh_3)_4$	2	80	K ₃ PO ₄	16	50

^a 5 mol% of catalysts were used.

^b 2.5 equiv. of bases were used.

^c Based on 9.



Scheme 2. Synthesis of (+)-cordiaquinone K. *Reagents, conditions and yields*. (a) TsCl, Py.; (b) NaI, acetone, reflux (96%, two steps); (c) (i) 2 equiv. *t*-BuLi, ether, -78° C; (ii) 2.5 equiv. B-MeO-9-BBN, hexane, THF; (iii) 3 M K₃PO₄; (iv) 5 mol% Pd(PPh₃)₄, 7, 80°C, 16 h (43%); (d) TBAF, THF, 60°C (74%); (e) PCC, MS4A, CH₂Cl₂ (63%); (f) CAN, CH₃CN, 0°C (quant.).

With the desired product (10) in hand (Scheme 1), the aromatic ring of 10 was oxidized with ceric ammonium nitrate (CAN) to afford (\pm)-13-deoxocordiaquinone K (5). The spectroscopic data of synthetic 5 are in perfect accordance with the structure of 5.¹⁷

According to the established methodology as described above, the synthesis of optically active cordiaquinone K was investigated (Scheme 2). The known alcohol¹⁸ (12) derived from the known ketoalcohol (11)¹⁹ was selected as the starting material. Alcohol 12 was converted to the corresponding iodide 13 in two steps (96%). The resulting iodide 13 was coupled with 7 by using the optimized conditions to give coupled product 14 in moderate yield (43%). After removal of the TBS group of 14 with TBAF at 60°C (74%), the resulting hydroxyl group was oxidized with PCC to give ketone 15 (63%). Finally, oxidation of the aromatic ring with CAN at 0°C for 30 min gave (S)-(+)-cordiaquinone K (4)²⁰ as a pale yellow gum in quantitative yield. The overall yield of (+)-1 was 19% in six steps from known alcohol (12). The ¹H and ¹³C NMR and MS spectra are identical with those of reported data.⁴ Synthetic cordiaquinone K (4) shows $[\alpha]_{D}^{26} = +44.9$ (c 0.35, acetone), while natural cordiaquinone K shows $[\alpha]_{\rm D} = -46.4$ (c 0.35, acetone).⁴ This means that our synthetic cordiaquinone K is the antipode of the natural product. The absolute configuration of natural cordiaquinone K is, therefore, determined to be R.

In conclusion, the total synthesis of (+)-cordiaquinone K was achieved by using one-pot B-alkyl Suzuki-Miyaura coupling reaction. The absolute configuration of natural cordiaquinone K was confirmed to be *R*. Further synthetic studies of other cordiaquinones or terpennoids employing this methodology are in progress.

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- 16. Representative procedure for the synthesis of (\pm) -10: To a stirred and cooled (-78°C) solution of 9 (97 mg, 0.35 mmol) in dry ether (5 ml) was added dropwise 530 µl of tert-BuLi (1.4 M in pentane, 0.75 mmol) under Ar. After stirring for 3 min, 820 µl of B-methoxy-9-borabicyclo[3.3.1]-nonane (1 M in hexane, 0.82 mmol) was added dropwise, followed by addition of dry THF (5 ml). After stirring for 10 min. at the same temperature, the resulting solution was allowed to warm to rt for 75 min. To the mixture, 3 M K₃PO₄ solution 0.27 ml (0.80 mmol) was added, followed by a solution of 7 (85 mg, 0.32 mmol) in DMF (5 ml). After addition of Pd(PPh₃)₄ (18 mg, 0.016 mmol), the mixture was stirred at 80°C for 16 h. After cooling to rt, the mixture was diluted with ether. The organic layer was washed with water and brine, and the combined aqueous layers were extracted with ether three times. The combined organic layers were dried with Na₂SO₄. After concentration in vacuo, the residue was chromatographed on silica gel (SiO₂: 8 g, hexane) to give 65 mg of (\pm) -10 (55%). Properties of (\pm) -10: colorless amorphous solid; IR (KBr) v_{max} (cm⁻¹)=3080 (m, H-C=C), 2920 (s, C-H), 1645 (m), 1635 (m), 1610 (s, Ar-O-CH3), 1460 (s), 1390 (s), 1345 (m), 1270 (s), 1165 (m), 1090 (m), 1000 (m), 970 (m), 895 (s), 825 (s), 795 (s), 715 (m); ¹H NMR (400 MHz, CDCl₃): $\delta = 0.81$ (s, 3H, 6"-CH₃), 0.89 (s, 3H, 6"-CH₃), 1.71-1.99 (m, 7H, 2',4",5"-CH₂), 2.05 (m, 1H, 3"-CHH), 2.06 (m, 1H, 3"-CHH), 2.50 (m, 1H, 1'-CHH), 2.75 (m, 1H, 1'-CHH), 3.93, 3.94 (2×s, 6H, 2×CH₃-O), 4.64 (br.s, 1H, H–C=C), 4.83 (br.s, 1H, H-C=C), 6.60, 6.66 (d, J=8.6 Hz, 2H, 2,3-H), 7.29 (dd, J=2.0, 8.8 Hz, 1H, 7-H), 7.94 (d, J=2.9 Hz, 1H)5-H), 8.07 (d, J=8.8 Hz, 1H, 8-H); ¹³C NMR (100 MHz, CDCl₃): $\delta = 23.7, 26.4, 28.3, 28.7, 32.4, 34.88, 34.93, 36.1,$ 53.9, 55.70, 55.70, 102.3, 103.2, 109.3, 120.2, 121.7, 124.7,

126.4, 127.3, 141.0, 149.19, 149.23, 149.6; HRFABMS: calcd for $C_{23}H_{30}O_2$ [M]⁺: 338.2246; found: 338.2243.

- 17. Properties of (±)-5: pale yellow gum; IR (film) ν_{max} (cm⁻¹)=3070 (w, H–C=C), 2930 (s, C–H), 2860 (m, C–H), 1670 (s, C=O), 1600 (s), 1450 (m), 1390 (w), 1370 (m), 1305 (s), 1140 (w), 1045 (m), 890 (m), 835 (m), 735 (m); ¹H NMR (400 MHz, CDCl₃): δ =0.82 (s, 3H, 19-CH₃), 0.89 (s, 3H, 18-CH₃), 1.22–1.80 (m, 7H, 10,13,14-CH₂, 11-H), 2.05 (m, 2H, 15-CH₂), 2.50 (m, 1H, 9-CHH), 2.14 (m, 1H, 9-CHH), 4.60 (br.s, 1H, H–C=C), 4.84 (br.s, 1H, H–C=C), 6.93 (s, 2H, 2,3-H), 7.52 (dd, *J*=1.5, 8.3 Hz, 1H, 7-H), 7.86 (d, *J*=1.5 Hz, 1H, 5-H), 7.97 (d, *J*=8.3 Hz, 1H, 8-H); ¹³C NMR (100 MHz, CDCl₃): δ =23.6, 26.5, 28.1, 28.3, 32.2, 34.8, 34.9, 35.9, 53.8, 109.7, 126.1, 126.7, 129.9, 131.2, 134.1, 138.5, 138.8, 148.7, 150.5, 184.9, 185.5; HRFABMS: calcd for C₂₁H₂₄O₂ [M]⁺: 308.1777; found: 308.1810.
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- 20. Properties of synthetic (+)-cordiaquinone K (4): pale yellow gum; $[\alpha]_{D}^{26} = +44.9$ (*c* 0.35, acetone); IR (film) v_{max} $(cm^{-1}) = 3080$ (w, H–C=C), 2950 (s, C–H), 2850 (s, C–H), 1710 (s, C=O), 1670 (m), 1600 (s), 1420 (s), 1310 (m), 935 (m), 900 (m); ¹H NMR (400 MHz, acetone- d_6): $\delta = 0.99$ (s, 3H, 19-CH₃), 1.18 (s, 3H, 18-CH₃), 1.49 (m, 1H, 10-CHH), 1.94 (m, 1H, 10-CHH), 2.24 (m, 1H, 14-CHH), 2.34 (dd, J=3.7, 12.0 Hz, 1H, 11-H), 2.55-2.98 (m, 5H, 9,15-CH₂, 14-CHH), 4.94 (br.s, 1H, H-C=C), 5.13 (br.s, 1H, H–C=C), 6.88 (s, 2H, 2,3-H), 7.58 (dd, J=1.8, 6.4 Hz, 1H, 7-H), 7.71 (d, J=1.8 Hz, 1H, 5-H), 7.82 (d, J=7.8 Hz, 1H, 8-H); ¹³C NMR (100 MHz, acetone- d_6): $\delta = 21.6$ (C-19), 27.4 (C-18), 29.9 (C-10), 31.1 (C-15), 34.6 (C-9), 38.0 (C-14), 49.4 (C-12), 56.7 (C-11), 113.9 (C-17), 126.5 (C-5), 127.0 (C-8), 130.9 (C-8a), 132.9 (C-4a), 134.9 (C-7), 139.3 (C-3), 139.5 (C-2), 150.2 (C-6), 185.4 (C-4), 185.7 (C-1), 213.6 (C-13); HREIMS: calcd for C₂₁H₂₂O₃ [M]⁺: 322.1569; found: 322.1581.