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Total Synthesis of (-)-Cordiaquinone B

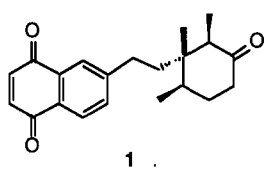
Takahiro Kuramochi, Morio Asaoka,* Taketoshi Ohkubo, and Hisashi Takei

Interdisciplinary Graduate School of Science and Engineering,Tokyo Institute of Technology,
Nagatsuta Midoriku, Yokohama 226, Japan

Abstract: Enantioselective synthesis of the unnatural antipode of cordiaquinone B possesing a 3-substituted 2,3,4-trimethylcyclohexanone framework was accomplished starting with (4*S*, 5*S*)-4-methyl-5-trimethylsilyl-2-cyclohexen-1-one. By this synthesis, the absolute structure of (+)-cordiaquinone B has been established. Copyright © 1996 Elsevier Science Ltd

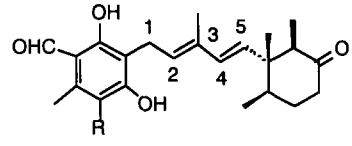
(+)-Cordiaquinone B is isolated from the root of *Cordia corymbosa* as the first example of a new type of merosesquiterpenoid quinone, exhibiting pronounced activity against gram-positive bacteria and mycobacteria.[1] A similar tetra-substituted cyclohexanone structure is presented in (-)-ascochlorin, antibiotic LL-Z1272e, and ilicolin C.[2] The absolute structures of the latter three compounds are established, however, that of (+)-cordiaquinone B is still unknown. In connection with our recent efforts for enantioselective syntheses of natural products with highly substituted cyclohexane moiety,[3] we were interested in the tetra-substituted cyclohexanone structure of **1** and targeted its enantioselective synthesis.

Figure 1



1 .

cordiaquinone B



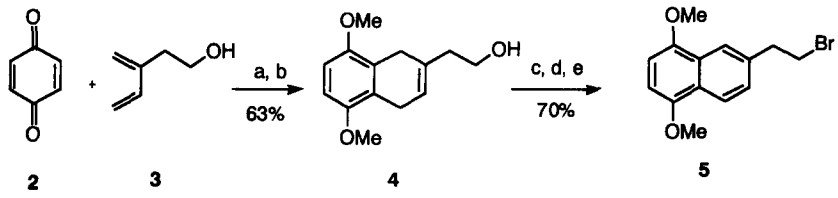
R = Cl ascochlorin

R = Cl , 4,5-dihydro ilicoline C

R = H , 4,5-dihydro antibiotic LL-Z1272ε

The protected naphthoquinone portion of **1** was prepared from benzoquinone and butadiene derivative **3** which was prepared by a reported procedure.[4] The Diels-Alder reaction between **2** and **3** in acetic acid at room temperature followed by a treatment with methyl orthoformate-methanol in the presence of *p*-toluenesulfonic acid gave **4** in 63% overall yield. Dehydrogenation with sulfur (1.05 eq) at 190°C for 10 min and the conversion of the resulting alcohol into bromide *via* tosylation and subsequent treatment with LiBr in acetone gave **5** in 70% overall yield.

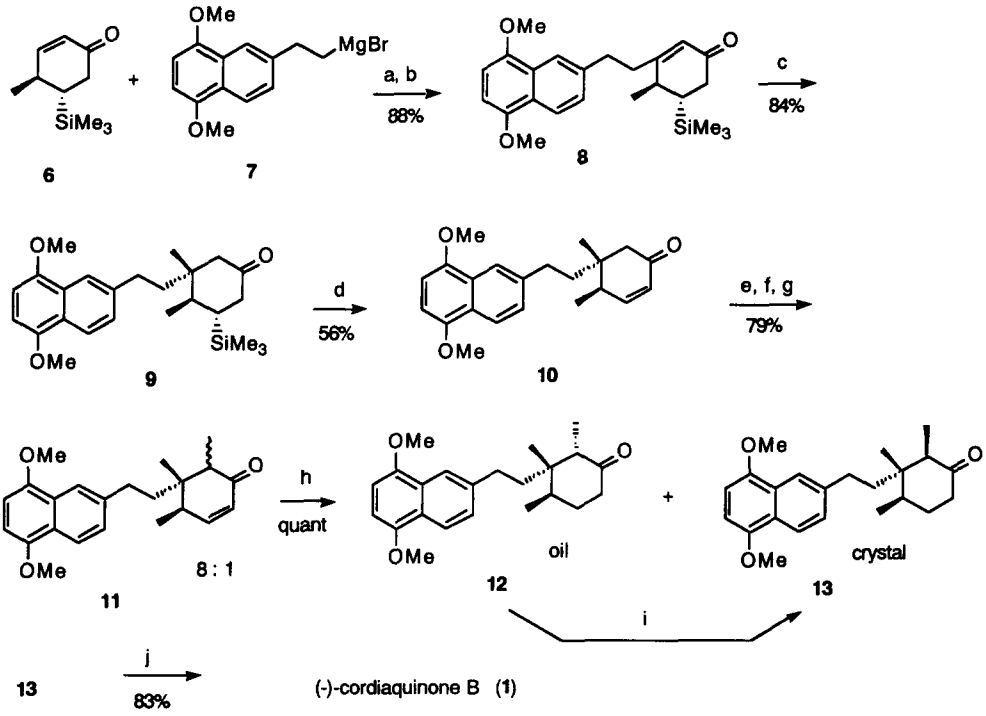
Scheme 1



a) AcOH, rt; b) $CH(OMe)_3$, MeOH, cat. TsOH; c) S, Δ; d) TsCl, PyH, e) LiBr

We had postulated that the cyclohexanone portion of (+)-cordiaquinone B would have the same absolute chemistry as natural metabolites of the ascochlorin series. Thus we initiated our synthesis with the previously prepared optically active enone **6**.[5]

Scheme 2



a) Me_3SiCl, HMPA, cat. $CuBrMe_2S$; b) $Pd(OAc)_2$; c) Me_2CuLi; d) $CuCl_2$, DMF; e) LDA, Me_3SiCl; f) MeLi; g) MeI; h) Pd-C, H_2; i) NaOH-MeOH; j) $K_2S_2O_8$, cat. $CuSO_4$, 70°C, 2h

1,4-Addition of the Grignard reagent **7** in the presence of chlorotrimethylsilane and HMPA[6] gave the corresponding enol silyl ether, which was subsequently treated with a stoichiometric amount of $Pd(OAc)_2$ to give the desired enone **8** in 88% overall yield. 1,4-Addition of Me_2CuLi to **8** gave the diastereomerically pure ketone **9** in 84% yield. The orientation of the methyl group on the quaternary carbon center was assigned based on the mechanistic consideration of model studies.[7] Initial trials for *in situ* methylation by trapping the intermediary enolate with methyl iodide resulted in a failure. Treatment of **9** with $CuCl_2$ in DMF at 85°C for 0.5 h gave the enone **10**[8] in 56% yield, whereby chlorinated products of **9**, which can be recycled by dechlorination with zinc in acetic acid, was also obtained. Since the direct methylation of **10** with LDA and methyl iodide was unsuccessful, enone **10** was first converted into the corresponding dienol silyl ether by the treatment with LDA and chlorotrimethylsilane. The lithium enolate generated by the treatment of the dienol silyl ether with MeLi successfully underwent methylation with MeI to give an approximately 8:1 diastereomeric mixture of the expected C6-epimeric cyclohexenones **11**[8] in 79% overall yield. The stereochemistry at the C6 position of the cyclohexenone was not clear at this stage. Hydrogenation of **11** in the presence of Pd-C catalyst gave an 8:1 diastereomeric mixture of the corresponding saturated ketones **12** and **13** in almost quantitative yield. In the ^1H NMR, the characteristic absorption of axial C3 methyl group with its chemical shift at high field (0.63 ppm) was found to be a minor component **13**. Thus, the structure of the major diastereomer [C3, C2, and C4 methyl groups at 1.00 (s), 1.04 (d), and 1.12 (d) ppm] was assigned as **12**. Base treatment (1.5 M NaOH-MeOH, rt for 2-3 h) of the mixture gave a 1:8 mixture of **12** (oil) and **13** (crystal). Although the two diastereomers were chromatographically inseparable, recrystallization gave pure **13**[8] (68%) which has the more stable natural product configuration. Oxidation of **13** with $K_2S_2O_8$ in the presence of a catalytic amount of $CuSO_4$ [9] gave (-)-(2*R*,3*S*,4*R*)-cordiaquinone B [$[\alpha]^{21}_D$ -9.36° (c 0.47, $CHCl_3$)] in 83% yield. The spectral and physical data except for the sense of optical rotation were perfectly identical with those of natural product. Thus the absolute structure of the natural (+)-cordiaquinone B [$[\alpha]^{20}_D$ +9.7° (c 0.4, $CHCl_3$)] was established as 2*S*, 3*R*,4*S*. Since the antipodal starting material is similarly accessible, this synthesis is equally applicable to the synthesis of natural enantiomer.

Acknowledgment. We thank Prof. Katsumi Kakinuma of Tokyo Institute of Technology for mass spectral determination.

References and Notes

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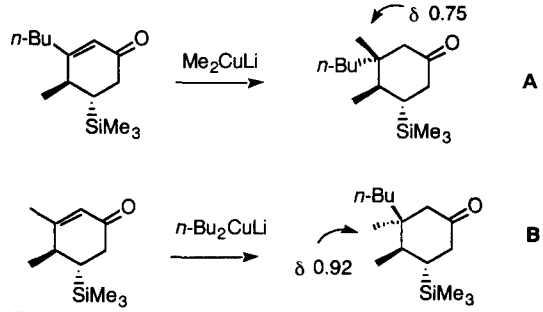
7. As a model study, both diastereomers **A** and **B** were synthesized in a highly diastereoselective manner as shown below, and their structures were assigned by ^{1}H NMR. The chemical shifts of the methyl groups on quaternary carbon centers appear at δ 0.75 (**A**) and 0.92 (**B**) respectively. That means the orientation of the methyl group of **A** occupies more shielded axial position. Consequently, 1,4-addition occurs from the opposite side of the trimethylsilyl groups.



8. Spectral data and specific rotations of (+)-**9**, (-)-**10** and (-)-**13** are shown below.

(+)-**9**: oil: [α]^{20}D +76.2° (*c* 4.5, $CHCl_3$) ; IR (neat) 1710 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 0.08 (s, 9H), 0.85 (s, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 1.12-1.23 (m, 1 H), 1.57-1.69 (m, 1 H), 1.75-1.90 (m, 2 H), 2.15 (dd, *J* = 2.15 and 12.7 Hz, 2 H), 2.27 (dq, *J* = 2.4 and 13.8 Hz, 1 H), 2.52 (d, *J* = 12.5 Hz, 1 H), 2.64-2.83 (m, 2 H), 3.95 (s, 3 H), 3.96 (s, 3 H), 6.64 (d, *J* = 8.6 Hz, 1 H), 6.69 (d, *J* = 8.3 Hz, 1 H), 7.33 (dd, *J* = 1.7 and 8.6 Hz, 1 H), 7.97 (d, *J* = 1.3 Hz, 1 H), 8.13 (d, *J* = 8.6 Hz, 1 H) ; ^{13}C NMR ($CDCl_3$) δ -1.6, 15.0, 19.0, 28.9, 30.2, 39.4, 43.1, 43.5, 44.3, 52.6, 55.6, 102.5, 103.3, 120.2, 122.1, 124.8, 126.5, 127.0 ,140.1, 149.1, 149.6, 213.2; HRMS calcd for $C_{25}H_{36}O_3Si$ 412.2434, found 412.2418.

(-)-**10**: oil: [α]^{21}D -20.8° (*c* 11.2, $CHCl_3$); IR (neat) 1675 cm^{-1}(C=O); ^{1}H NMR ($CDCl_3$) δ 0.98 (s, 3 H), 1.12 (d, *J* = 7.3 Hz, 3 H), 1.73-1.81 (m, 2 H), 2.43 (d, *J* = 4.6 Hz, 2 H), 2.53-2.63 (m, 1 H), 2.70 -2.78 (m, 2 H), 3.94 (s, 3 H), 3.96 (s, 3 H), 6.00 (dd, *J* = 2.5 and 10.1 Hz, 1 H), 6.62-6.71 (m, 3H), 7.32 (dd, *J* = 2.0 Hz and 8.6 Hz, 1 H), 7.96 (s, 1 H), 8.12 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 14.2, 20.0, 30.6, 39.1, 39.7, 43.0, 48.9, 55.7, 102.5, 103.4, 120.2, 122.1, 124.8, 126.5, 127.0, 128.0, 139.9, 149.1, 149.6, 154.7, 199.9; HRMS calcd for $C_{22}H_{26}O_3$ 338.1882, found 338.1862.

(-)-**13**: mp 170.5-171.5 °C : [α]^{21}D -5.6° (*c* 1.1, $CHCl_3$); IR (KBr) 1710 cm^{-1} (C=O); ^{1}H NMR ($CDCl_3$) δ 0.62 (s, 3 H), 1.02 (d, *J* = 6.6 Hz, 3 H), 1.05 (d, *J* = 6.6 Hz, 3 H), 1.59-1.81 (m, 3 H), 1.87-1.97 (m, 1 H), 2.13-2.27 (m, 1 H), 2.35-2.50 (m, 2 H), 2.60-2.72 (m, 2 H), 2.76-2.88 (m, 1 H), 3.95 (s, 3 H), 3.97 (s 3 H), 6.65 (d, *J* = 8.3 Hz, 1 H), 6.70 (d, *J* = 8.3 Hz, 1 H), 7.34 (dd, *J* = 1.7 and 8.6 Hz, 1 H), 7.97 (d, *J* = 1.0 Hz, 1 H), 8.13 (d, *J* = 8.6 Hz, 1 H); ^{13}C NMR ($CDCl_3$) δ 7.8, 15.2, 29.5, 31.0, 36.3, 39.5, 41.7, 43.8, 50.6, 55.7, 55.7, 102.5, 103.4, 120.1, 122.1, 124.8, 126.5, 127.0, 140.1, 149.1, 149.6, 213.8; HRMS calcd for $C_{23}H_{30}O_3$ 354.2195, found 354.2204.

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