# The absolute configuration and total synthesis of korormicin

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## Abstract

The marine antibiotic korormicin, isolated from the culture filtrate of marine bacterial strain *Pseudoalteromonas* sp. F-420, specifically inhibits the growth of marine Gram-negative bacteria without affecting terrestrial species. The absolute configuration of korormicin was determined by the combination of a CD exciton chirality method and chemical degradation. Convergent total synthesis of korormicin has been also achieved. © 1999 Elsevier Science Ltd. All rights reserved.

Korormicin (1) isolated from the culture filtrate of marine bacterial strain *Pseudoalteromonas* sp. F-420 specifically inhibits the growth of marine Gram-negative bacteria without affecting terrestrial species.[1] This unusual biological activity arises as a result of targeting the $Na^+$-translocating NADH-quinone reductase (NQR), an important membrane-bound enzyme in the respiratory system of marine Gram-negative bacteria. Non-competitive NQR inhibition by 1 is remarkably more potent and more selective than the known NQR inhibitor, 2-heptenyl-4-hydroxyquinoline *N*-oxide (HQNO).[2] Although the unique structure of korormicin has been established by spectroscopic methods, the stereochemistry remains unknown. These intriguing biological and structural features inspired our synthetic studies of 1. We describe herein the absolute stereochemistry and total synthesis of korormicin.[3]



**1, Korormicin**
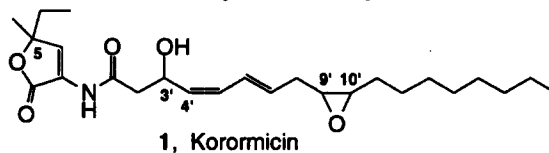
Since the four stereogenic centers in 1 are isolated from one another, each configuration was determined separately. First, we established the chirality of the allylic alcohol at C3′ by the CD exciton chirality method for the corresponding *p*-bromobenzoate (2) (Scheme 1).[4] The large ¹H NMR coupling constant $J_{3',4'}=10.3$ Hz in ethanol-$d_6$ showed that this *Z*-type allylic benzoate system of 2 takes virtually a single

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stable conformation as expected from allylic 1,3-strain,[5] i.e. antiperiplanar orientation between H3' and H4'; in other words, the dihedral angle O-C3'-C4'-C5' is about 120°. A large Cotton effect [EtOH, $\lambda_{ext}$ 246 nm ($\Delta\varepsilon$-21); $\lambda_{ext}$ 227 nm ($\Delta\varepsilon$+8)] (Fig. 1) coincides with this conformational analysis. The negative CD indicates a 3'$R$ configuration for 2.[4]



**1, Korormicin**

i

**2**

ii, iii

($S$)-(-)-3    +    ($S,R$)-(-)-4
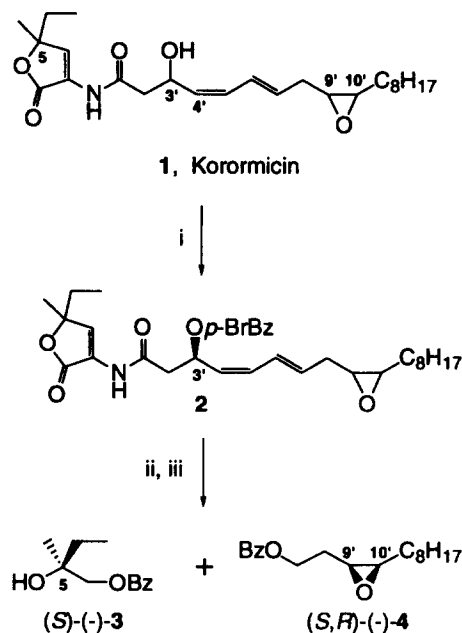
Scheme 1. *Reagents and conditions*: (i) $p$-BrBzCl, DMAP, Et$_3$N, CH$_2$Cl$_2$, rt, 5 h, 81%; (ii) O$_3$, MeOH, CH$_2$Cl$_2$, then NaBH$_4$, -80°C; (iii) BzCl, Et$_3$N, CH$_2$Cl$_2$, rt, 7 h

Degradation of 2 was then successfully carried out. Extensive ozonolysis of 2 followed by reduction with NaBH$_4$ and benzoylation gave hydroxy benzoate [($S$)-(-)-3] and *cis*-epoxybenzoate [($S,R$)-(-)-4] in ~20% and ~50% yields, respectively. The authentic enantiomers were synthesized in an enantio-defined manner as shown in Scheme 2.[6] Alkylation of enantiomerically pure Seebach's dioxolanone (*trans*-5) using LDA with iodoethane yielded 6 in 97% ds.[7] Reduction of 6 with LAH followed by
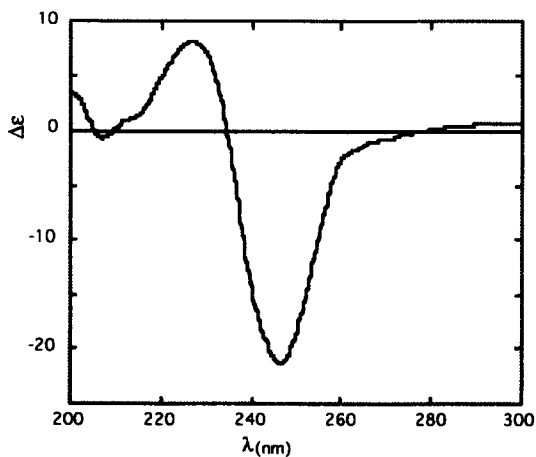


Figure 1. CD spectrum of 2 in EtOH

monoacylation of the resulting diol gave the benzoate (S)-(−)-3. The enantiomer [(R)-(+)-3] was also synthesized from cis-5. Syntheses of (S,R)-(−)-4 and (R,S)-(+)-4 were performed in a straightforward manner from epoxyalcohol (8) and its enantiomer, respectively (Scheme 3), which were prepared by Sharpless asymmetric epoxidation.[8] Synthesized (S)-(−)-3 and (S,R)-(−)-4 are identical in every respect including HPLC profile (CHIRALCEL OD, Daicel) with the samples degraded from natural korormicin, respectively. Consequently, the absolute stereochemistry of korormicin is assigned as $5S,3'R,9'S,10'R$ (Fig. 2).
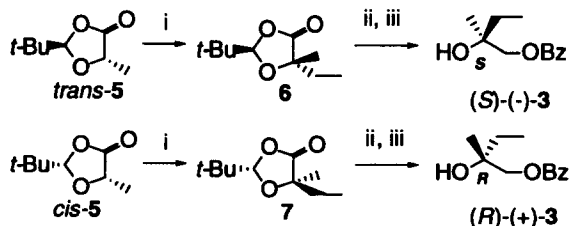


Scheme 2. *Reagents and conditions*: (i) LDA, THF, −80°C, 40 min, then EtI, to −20°C, 3 h, ~83%; (ii) LAH, Et₂O, rt, 5 h; (iii) BzCl, Py, (CHCl₂)₂, rt, 40 min, ~57% (two steps)
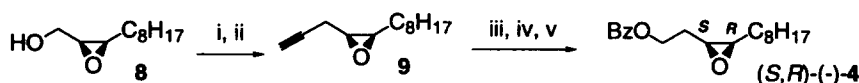


Scheme 3. *Reagents and conditions*: (i) Tf₂O, 2,6-lutidine, CH₂Cl₂, −20°C; (ii) lithium acetylide, THF, DMPU, −80 to 0°C, 10 h, 46% (two steps); (iii) Lindlar's cat., H₂, AcOEt, rt, 15 min; (iv) O₃, MeOH, CH₂Cl₂, −70°C, 10 min, then NaBH₄, to rt, 17% (two steps); (v) BzCl, Py, (CH₂Cl)₂, rt, 5 h, 34%

Having determined the absolute configuration, we set out in the synthesis of korormicin (1). Strategic bond disconnection is outlined in Fig. 3. Novel α-amino-α,β-unsaturated butyrolactone (13) was synthesized concisely as shown in Scheme 4. Reduction of 6 with DIBAL-H and methanolysis of the resulting lactol gave α-hydroxyaldehyde (10). Aldol condensation of 10 with an enolate of the Shiff base glycine ester (11)[9] resulted in the direct formation of lactone (12). Hydrolysis of the imine (12) under mild acidic conditions gave amine (13).

Syntheses of E-alkenylstannane (15) and Z-vinyl iodide (18) as the substrates for Stille coupling[10] are shown in Scheme 5. Although hydrostannation using Bu₃SnH and stannylcupration[11] of 9 resulted in non-selective formation of inseparable regioisomers (E:Z=1.4–3.5:1 and E:1,1-disubstituted=1:1),
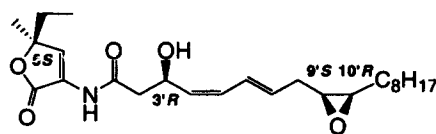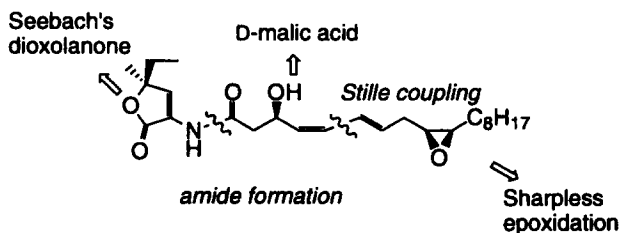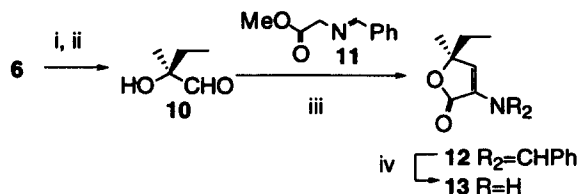


Figure 2.



Figure 3. Strategic bond disconnection of koromicin (1)

Scheme 4. *Reagents and conditions*: (i) DIBAL, CH$_2$Cl$_2$, −70 to −60°C, 20 min, 83%; (ii) K$_2$CO$_3$, dry MeOH, rt, 2 h, 55%; (iii) 11, LDA, THF, HMPA, −80 to 10°C, 6 h, 35%; (iv) AcOH:THF:H$_2$O (1:40:20), 0°C to rt, 3 h, 83%

palladium-catalyzed hydrostannation[12] of 1-bromoalkyne (**14**) yielded *E*-vinylstannane (**15**) selectively (*E*:*Z*=7:1). Synthesis of **18** was initiated with diol (**16**) prepared from D-malic acid.[13] Selective protection, and then oxidation followed by Wittig olefination[14] gave the *Z*-vinyl iodide (**18**) as a major isomer (7:1). The following reactions were performed without separation of geometrical isomers for **15** and **18**, because the isomers of **1** were separable at the final stage. Coupling reaction of **15** with **18** under modified Stille conditions using tri-2-furylphosphine[15] gave *E,Z*-diene (**19**). Removal of the TBS group of **19** using TBAF followed by saponification gave carboxylic acid (**20**). Condensation of **20** with the amine (**13**) using EDC·HCl and HOAT yielded korormicin (**1**). The geometrical isomers were separated by HPLC; synthetic **1** is identical to the natural product ($^1$H, $^{13}$C NMR, IR, UV, CD, MALDI TOF-MS, [α]$_D$).[16]
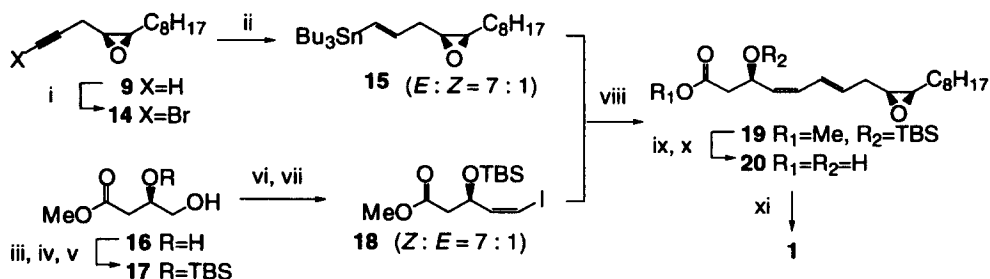


Scheme 5. *Reagents and conditions*: (i) NBS, AgNO$_3$, acetone, 71%; (ii) PdCl$_2$(PPh$_3$)$_2$, Bu$_3$SnH, THF, rt, 10 min, 29%; (iii) TrCl, Py, DMAP, rt, 1 d; (iv) TBSCl, imidazole, DMF, rt, 1 h, 93% (two steps); (v) Et$_2$AlCl, CH$_2$Cl$_2$, −80 to −60°C, 40 min, 84%; (vi) (COCl)$_2$, DMSO, Et$_3$N, CH$_2$Cl$_2$, −80 to −50°C, 30 min; (vii) (Ph$_3$P$^+$CH$_2$I)I$^-$, NaHMDS, THF, HMPA, −100 to 0°C, 2 h, 55% (two steps); (viii) Pd$_2$(dba)$_3$·CHCl$_3$, (2-furyl)$_3$P, NMP, rt, 6 d, 34%; (ix) TBAF, THF, rt, 6 h, 78%; (x) LiOH aq., MeOH, rt, 6.5 h, 81%; (xi) **13**, EDC·HCl, HOAt, DMF, rt, 10 h, 42%

In conclusion, we could unambiguously determine the absolute configuration of korormicin. Further synthesis of isomers and the structure–activity relationship study are in progress in our laboratory.

## Acknowledgements

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16. Synthetic **1**: $[\alpha]_D^{32}$ −23 (*c* 0.065, EtOH) {natural **1**:[1] $[\alpha]_D^{26}$ −24.4 (*c* 0.065, EtOH)}; CD $\lambda_{ext}$ 247 nm ($\Delta\varepsilon$−4.0) [natural **1**: $\lambda_{ext}$ 246 nm ($\Delta\varepsilon$−4.7)].