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The absolute configuration and total synthesis of korormicin

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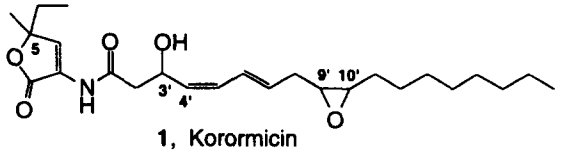
Abstract

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.

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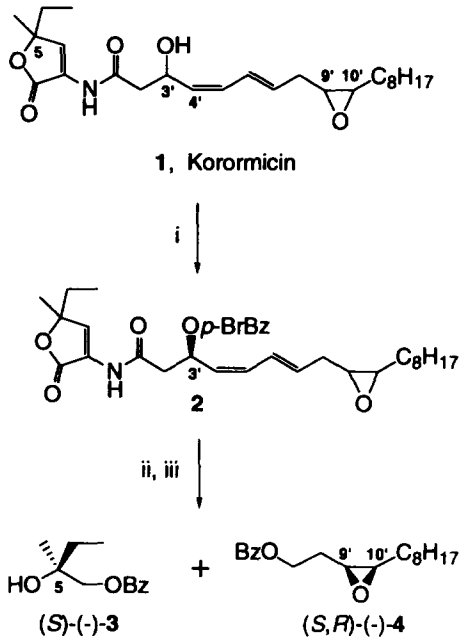
stable conformation as expected from allylic 1,3-strain,[5] i.e. antiperiplanar orientation between H3′ and H4′; in other words, the dihedral angle O-C3′-C4′-C5′ is about 120°. A large Cotton effect [EtOH, λ_{ext} 246 nm ($\Delta\varepsilon$-21); λ_{ext} 227 nm ($\Delta\varepsilon$+8)] (Fig. 1) coincides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



Scheme 1. *Reagents and conditions*: (i) *p*-BrBzCl, DMAP, Et_3N, CH_2Cl_2, rt, 5 h, 81%; (ii) O_3, MeOH, CH_2Cl_2, then $NaBH_4$, −80°C; (iii) BzCl, Et_3N, CH_2Cl_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 enantiodefined 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

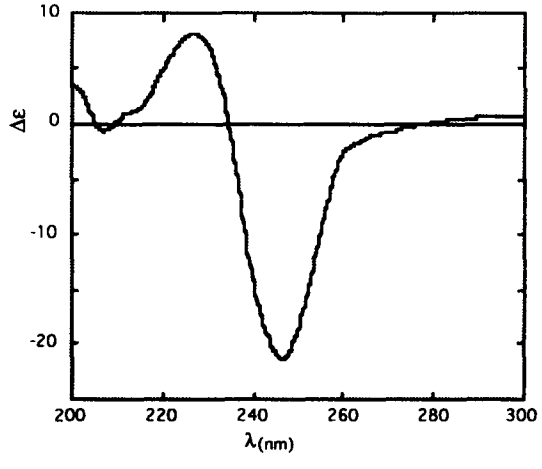
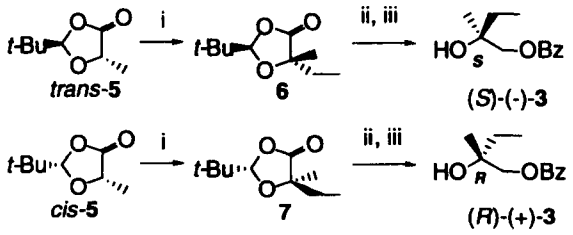
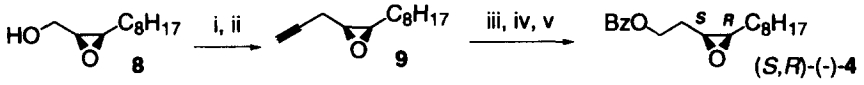


Figure 1. CD spectrum of **2** in EtOH

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 5*S*,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, Et_2O, rt, 5 h; (iii) BzCl, Py, $(CHCl_2)_2$, rt, 40 min, ~57% (two steps)



Scheme 3. *Reagents and conditions*: (i) Tf_2O, 2,6-lutidine, CH_2Cl_2, −20°C; (ii) lithium acetylide, THF, DMPU, −80 to 0°C, 10 h, 46% (two steps); (iii) Lindlar's cat., H_2, AcOEt, rt, 15 min; (iv) O_3, MeOH, CH_2Cl_2, −70°C, 10 min, then $NaBH_4$, to rt, 17% (two steps); (v) BzCl, Py, $(CH_2Cl)_2$, 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 Bu_3SnH 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),

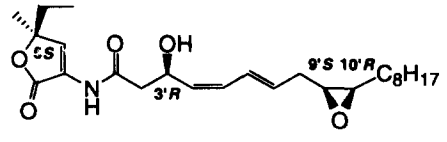


Figure 2.

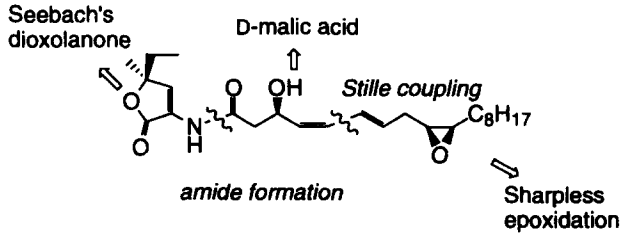
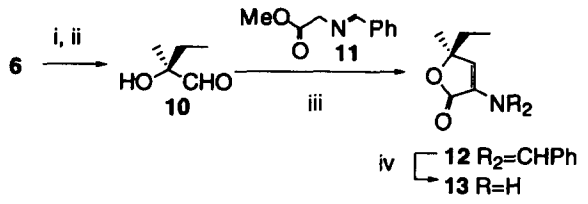
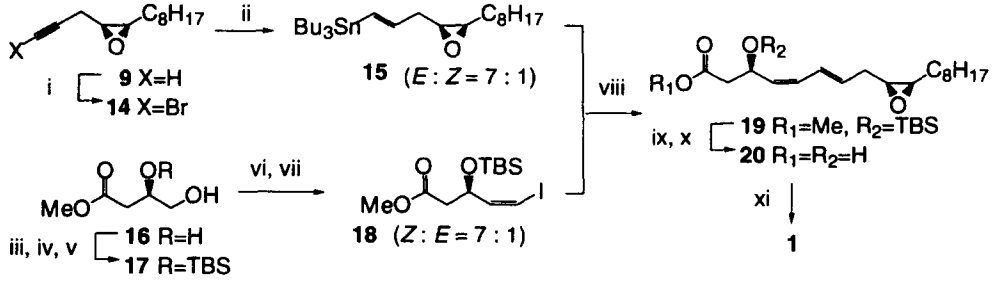


Figure 3. Strategic bond disconnection of koromicin (**1**)



Scheme 4. *Reagents and conditions*: (i) DIBAL, CH_2Cl_2, −70 to −60°C, 20 min, 83%; (ii) K_2CO_3, dry MeOH, rt, 2 h, 55%; (iii) **11**, LDA, THF, HMPA, −80 to 10°C, 6 h, 35%; (iv) AcOH:THF:H_2O (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 (^1H, ^{13}C NMR, IR, UV, CD, MALDI TOF-MS, $[\alpha]_D$).[16]



Scheme 5. *Reagents and conditions*: (i) NBS, $AgNO_3$, acetone, 71%; (ii) $PdCl_2(PPh_3)_2$, Bu_3SnH, THF, rt, 10 min, 29%; (iii) TrCl, Py, DMAP, rt, 1 d; (iv) TBSCl, imidazole, DMF, rt, 1 h, 93% (two steps); (v) Et_2AlCl, CH_2Cl_2, −80 to −60°C, 40 min, 84%; (vi) $(COCl)_2$, DMSO, Et_3N, CH_2Cl_2, −80 to −50°C, 30 min; (vii) $(Ph_3P^+CH_2I)I^-$, NaHMDS, THF, HMPA, −100 to 0°C, 2 h, 55% (two steps); (viii) $Pd_2(dba)_3 \cdot CHCl_3$, (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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References

1. Yoshikawa, K.; Takadera, T.; Adachi, K.; Nishijima, M.; Sano, H. *J. Antibiot.* **1997**, *50*, 949.
2. Yoshikawa, K.; Nakayama, Y.; Hayashi, M.; Unemoto, T.; Mochida, K. *J. Antibiot.* **1999**, *52*, 182.
3. Kobayashi, Y.; Nakayama, Y.; Yoshida, S. unpublished results. We thank Prof. Y. Kobayashi (Tokyo Institute of Technology) for informing us of their work before submitting their manuscript.

4. Gonnella, N. C.; Nakanishi, K.; Martin, V. S.; Sharpless, K. B. *J. Am. Chem. Soc.* **1982**, *104*, 3775.
5. (a) Hoffmann, R. W. *Chem. Rev.* **1989**, *89*, 1841; (b) Johnson, F. *Chem. Rev.* **1968**, *68*, 375.
6. Asymmetric dihydroxylation (Sharpless, K. B.; Amberg, W.; Bennani, Y. L.; Crispino, G. A.; Hartung, J.; Jeong, K.-S.; Kwong, H.-L.; Morikawa, K.; Wang, Z.-M.; Xu, D.; Zhang, X.-L. *J. Org. Chem.* **1992**, *57*, 2768) of 2-methyl-1-butene using $(DHQD)_2$–PHAL/OsO_4 and $(DHQ)_2$–PHAL/OsO_4 followed by benzoylation gave unsatisfactory enantiomeric excess: (*R*)-**3**, 55% ee; (*S*)-**3**, 46% ee, respectively.
7. Seebach, D.; Naef, R.; Calderari, G. *Tetrahedron* **1984**, *40*, 1313.
8. Gao, Y.; Hanson, R. M.; Klunder, J. M.; Ko, S. Y.; Masamune, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1987**, *109*, 5765.
9. Bey, P.; Vevert, J. P. *Tetrahedron Lett.* **1977**, *18*, 1455.
10. Stille, J. K.; Groh, B. L. *J. Am. Chem. Soc.* **1987**, *109*, 813.
11. Betzer, J.-F.; Delaloge, F.; Muller, B.; Pancrazi, A.; Prunet, J. *J. Org. Chem.* **1997**, *62*, 7768.
12. Zhang, H. X.; Guibe, F.; Balavoine, G. *J. Org. Chem.* **1990**, *55*, 1857.
13. Saito, S.; Ishikawa, T.; Kuroda, A.; Koga, K.; Moriwake, T. *Tetrahedron* **1992**, *48*, 4067.
14. (a) Stork, G.; Zhao, K. *Tetrahedron Lett.* **1989**, *30*, 2173; (b) Seyferth, D.; Heeren, J. K.; Singh, G.; Grim, S. O.; Hughes, W. B. *J. Organomet. Chem.* **1966**, *5*, 267.
15. Farina, V.; Krishnan, B. *J. Am. Chem. Soc.* **1991**, *113*, 9585.
16. Synthetic **1**: $[\alpha]_D^{32}$ –23 (*c* 0.065, EtOH) {natural **1**:[1] $[\alpha]_D^{26}$ –24.4 (*c* 0.065, EtOH)}; CD λ_{ext} 247 nm ($\Delta\varepsilon$–4.0) [natural **1**: λ_{ext} 246 nm ($\Delta\varepsilon$–4.7)].