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Determination of the stereoisomer of korormicin from eight possible stereoisomers by total synthesis

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Abstract

Possible diastereoisomers of korormicin were synthesized in a stereoselective manner, and the absolute stereochemistry of natural korormicin was elucidated by comparison of the reported $[\alpha]_D$ value with the measured ones.

Keywords: alkenyl halides; asymmetric synthesis; boron; boron compounds; korormicin; nickel; nickel compounds.

Korormicin, isolated by Yoshikawa in 1997 from the marine bacterium, *Pseudoalteromonas* sp. F-420, inhibits the growth of marine Gram-negative bacteria strongly and specifically, while it is inactive against terrestrial microorganisms.[1] According to the authors, the biological specificity is useful for classification of marine bacteria. In addition, korormicin might be important as a lead compound in the development of effective drugs for fish in aquaculture against diseases caused by Gram-negative bacteria. Planar structure **1** is determined by the authors using NMR spectroscopy. Consequently, the absolute configuration should be urgently elucidated for the next step in research work toward the goal mentioned above. Among data reported for korormicin, the ^{1}H NMR and ^{13}C NMR spectra in DMSO-d_6 and the specific rotation ($[\alpha]^{26}_D$) of −24.4 (*c* 0.29, EtOH) are, in principle, useful for facile determination of the natural stereoisomer. Since the stereochemistry of the epoxide and the conjugated diene is established, eight diastereomers exist in total. Herein, we report the first and stereoselective synthesis of the diastereoisomers and elucidation of the isomer corresponding to natural korormicin.

Based on a useful reaction for the construction of *cis*,*trans* conjugated dienes with a bulky group at the end of the *cis* olefin-side using *cis* vinyl iodides and *trans* borates,[2] we envisioned that condensation of α-enamino lactone **2** with the known *cis* vinyl iodide **3**[3] and subsequent coupling reaction between the condensation product **4** and borate **6** (derived from the boronate ester **5** and MeLi) would provide **1** (Scheme 1).

Preliminarily, racemic fragments **2**, **3**, and **5** (preparation of racemic **2** and **5** is not shown) were used to ensure the route. Condensation of **2** and **3** with DCC (1.2 equiv.) in the presence of DMAP (0.2

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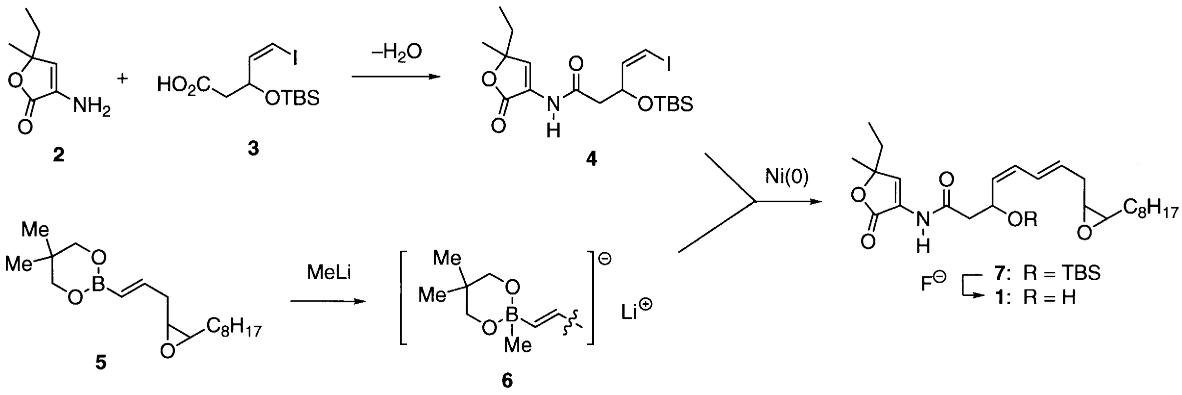
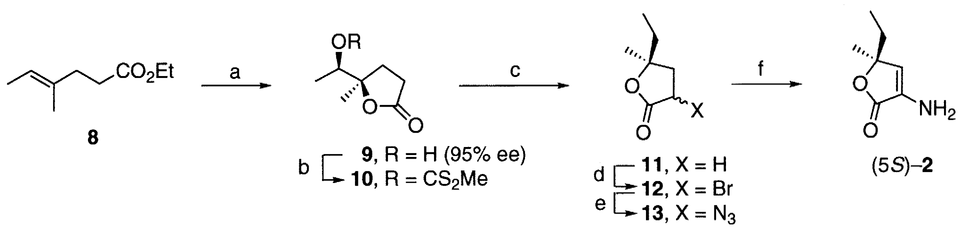


Scheme 1. Strategy for synthesis of korormicin

equiv.) and PPTS[4] (0.3–0.5 equiv.) in CH_2Cl_2 afforded amide **4** in 70–75%. In order to accomplish the coupling reaction, MeLi (1.6 equiv.) was added to a mixture of **5** (1.4 equiv.) and $NiCl_2(PPh_3)_2$ (0.15 equiv.) in THF to produce in situ a Ni(0) species and **6**, and a reaction with iodide **4** at room temperature for 4 h provided TBS ether **7** stereoselectively. Finally, deprotection with Bu_4NF afforded a mixture of diastereomers of **1** in 35% yield from **4**. The ^{1}H NMR (300 MHz) and ^{13}C NMR spectra of synthetic **1** in DMSO-d_6 were fully coincidental with the data reported for natural **1**.[1a]

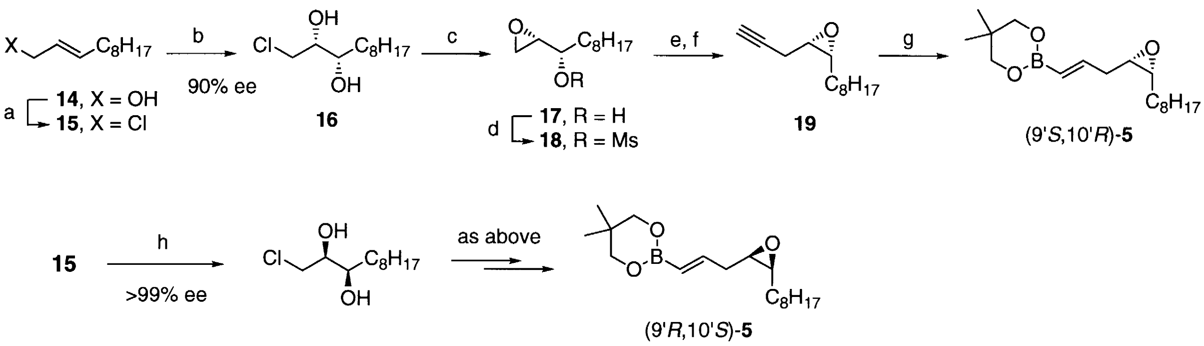
We then carefully checked these data and those in $CDCl_3$ in order to find out any peak(s) which are diagnostic for determination of the stereostructure. Some signals were actually split in the expanded ^{13}C NMR spectrum, but only into two lines ($\Delta\delta$ <0.2 ppm). This finding is apparently insufficient to distinguish the four detectable diastereomers.[5,6] Consequently, we undertook synthesis of all the stereoisomers of **1** to compare the $[\alpha]_D$ values. Our strategy focused on the Sharpless asymmetric dihydroxylation (AD) reaction[7] for construction of the necessary chiral centers. Since the $[\alpha]_D$ of the four diastereomers is, in principle, sufficient to determine the stereostructure, four (5*S*) diastereomers of **1**, i.e., the isomers possessing (5*S*,3′*R*,9′*S*,10′*R*), (5*S*,3′*S*,9′*S*,10′*R*), (5*S*,3′*S*,9′*R*,10′*S*), and (5*S*,3′*R*,9′*R*,10′*S*) configurations, respectively, were prepared.[8]

For preparation of α-enamino lactone (5*S*)-**2**, AD reaction[7b,c] of known **8**[9] with AD-mix-β afforded the diol, which, under the conditions, cyclized spontaneously to yield lactone **9** in 95% ee[10] (Scheme 2). The hydroxyl group of **9** was removed by the standard method[11] via xanthate ester **10** to afford lactone **11** in 75% yield from **8**. α-Bromination of lactones was accomplished by enolate-trap of the lithium enolate, prepared from **11** and LDA, with TMSCl and subsequent reaction with Br_2 in 85% yield. Reaction of bromide **12** with NaN_3 in hot EtOH overnight afforded azide **13**, which, upon treatment[12] with NaOEt in EtOH, produced (5*S*)-**2** in 82% yield from **12**.



Scheme 2. Preparation of enaminolactone (*S*)-**2**: (a) AD-mix-β, $MeSO_2NH_2$; (b) imidazole, NaH, CS_2 then MeI, 82% from **8**; (c) Bu_3SnH, AIBN, toluene, reflux, 92%; (d) (i) LDA, −70°C; (ii) TMSCl; (iii) Br_2; (e) NaN_3, EtOH; (f) NaOEt, EtOH, 58% from **11**

The (9′*S*,10′*R*)-enantiomer of **5** was prepared by a route summarized in Scheme 3. Alcohol **14**[13] was first converted into chloride **15**. Sharpless AD reaction[7d] of **15** with AD-mix-α afforded diol **16**, which, upon reaction with crushed NaOH in THF, gave **17** (90% ee)[10] in 84% yield. Mesylation of **17** and subsequent epoxide ring opening[14] with the reagent derived from TMSC≡CLi and $BF_3 \cdot OEt_2$ furnished the corresponding alcohol, which, on treatment with K_2CO_3 in MeOH, produced **19** in 69% yield via concomitant desilylation and epoxide ring formation. Finally, acetylene **19** was converted into (9′*S*,10′*R*)-**5** stereoselectively in 64% yield by hydroboration with $(Ipc)_2BH$[15] followed by oxidation with MeCHO and subsequent ligand exchange of the diethyl boronate with 2,2-dimethyl-1,3-propanediol. Similarly, AD reaction of **15** with AD-mix-β followed by reaction with NaOH produced the enantiomer of **17** with >99% ee,[10] which was then transformed into (9′*R*,10′*S*)-**5** stereoselectively with a comparable yield for each step.



Scheme 3. Preparation of (9′*S*,10′*R*) and (9′*R*,10′*S*) enantiomers of **5**: (a) CCl_4, PPh_3, 81%; (b) AD-mix-α, $MeSO_2NH_2$; (c) NaOH, THF, 84% from **15**; (d) MsCl, NEt_3; (e) (i) TMSC≡CH, *n*-BuLi; (ii) $BF_3 \cdot OEt_2$; (iii) **18**; (f) K_2CO_3, MeOH, 69% from **17**; (g) (i) $(Ipc)_2BH$; (ii) MeCHO, reflux; (iii) $HOCH_2C(Me)_2CH_2OH$, 64%; (h) AD-mix-β, $MeSO_2NH_2$

The condensation reaction of (5*S*)-**2** (95% ee) with (3′*R*)- and (3′*S*)-**3** (both 99% ee), which were prepared by the literature procedure,[3] was carried out once again under the conditions (vide supra) to afford (5*S*,3′*R*)- and (5*S*,3′*S*)-**4**, respectively, in 77–82% yields. Each of the stereoisomers was then submitted to the coupling with (9′*S*,10′*R*)-**5** (90% ee) and (9′*R*,10′*S*)-**5** (>99% ee), respectively, to furnish the stereoisomers of **7**,[16] which, upon desilylation with Bu_4NF, produced the four diastereoisomers of **1** totally in 48–53% yields from **4**.

The stereostructures of **1** thus synthesized are presented in Fig. 1 with the $[\alpha]_D$ values corrected[17] for the pure stereoisomers by linear calculation of the measured $[\alpha]_D$ values (shown in parentheses) taking into consideration of the *R*/*S* chirality ratio at each of the chiral centers. Among them, the value (−24.5) obtained from the (5*S*,3′*R*,9′*S*,10′*R*)-isomer is closest to that reported for the natural product (−24.4) and the other values are out of the range of error of ±2 degrees, hence the isomer is definitely natural korormicin.[18,19]

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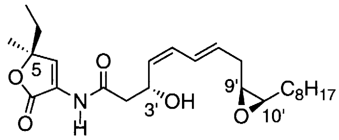

(5*S*,3'*R*,9'*S*,10'*R*)-**1**
$[\alpha]^{30}_{D}$ = −24.5 (*c* 0.828, EtOH)
(−24)

(5*S*,3'*S*,9'*S*,10'*R*)-**1**
$[\alpha]^{30}_{D}$ = −12.1 (*c* 0.844, EtOH)
(−12)

(5*S*,3'*S*,9'*R*,10'*S*)-**1**
$[\alpha]^{29}_{D}$ = −16.9 (*c* 1.27, EtOH)
(−16)

(5*S*,3'*R*,9'*R*,10'*S*)-**1**
$[\alpha]^{26}_{D}$ = −29.6 (*c* 1.04, EtOH)
(−28)

Fig. 1. Specific rotations ($[\alpha]_D$) for the given stereoisomers of **1**, which were calculated from the measured $[\alpha]_D$ values shown in parentheses based on the *R*/*S* chirality ratio at each of the chiral centers

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5. The C(8) Me group in the ^{1}H NMR spectrum of **7** appeared as two singlets (δ 1.46 and 1.47). Some peaks in the expanded ^{13}C NMR spectrum of **7** were also insufficiently separated ($\Delta\delta$ <0.2 ppm).
6. Only one spot was seen on TLC.
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8. Specific rotation ($[\alpha]_D$) of the other four diastereomers with (*R*) chirality at C(5) should have, in principle, the reverse rotations of those chosen for the preparation, respectively.
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16. (5*S*,3′*R*,9′*S*,10′*R*)-**7** (TBS ether of natural korormicin): IR (neat) 3321, 1765, 1701, 1655, 837, 779 cm^{-1}; ^{1}H NMR ($CDCl_3$) δ 0.04 (s, 3H), 0.05 (s, 3H), 0.8–0.9 (m, 15H), 1.47 (s, 3H), 1.1–1.6 (m, 12H), 1.70–1.88 (m, 2H), 2.24–2.59 (m, 4H), 2.92–3.00 (m, 2H), 4.95–5.04 (m, 1H), 5.35 (dd, *J*=11, 8 Hz, 1H), 5.78 (dt, *J*=15, 7 Hz, 1H), 5.97 (t, *J*=11 Hz, 1H), 6.39 (dd, *J*=15, 11 Hz, 1H), 7.33 (s, 1H), 8.15 (br s, 1H); ^{13}C NMR ($CDCl_3$) δ 169.9, 169.3, 133.8, 132.3, 131.3, 129.0, 126.9, 124.9, 88.3, 66.6, 57.1, 55.9, 45.9, 32.0, 31.8, 31.5, 29.51, 29.50, 29.2, 27.7, 26.6, 25.7, 24.4, 22.6, 18.0, 14.1, 8.1, −4.4, −5.2.
17. The difference is ca. one degree in each case and hence it is not necessary to consider equivocal separation of the minor diastereomer by chromatography during the synthesis.
18. Our result was presented at the Annual Meeting of the Chemical Society of Japan, March 31, 1999 (4A2 10 and 4A2 11).
19. Determination of the absolute stereochemistry of **1** by using the degradation products and a synthesis of natural **1** were presented at the same meeting: Uehara, H.; Oishi, T.; Hirama, M.; Yoshikawa, K.; Mochida, K. Presented at the Annual Meeting of the Chemical Society of Japan, March 31, 1999 (4A2 09).