Short Communication

Total Synthesis of (+)- and (-)-Coronafacic Acid

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Coronatine (1), a phytotoxin produced by *Pseudomonas coronafaciens* var. *atropurpurea*, induces chlorosis on the leaves of Italian rye grass and also expands potato cells at a low concentration.¹⁾ The structure and the absolute configuration of 1 have been determined by Ichihara *et al.*,²⁾ and the partial synthesis of 1 was achieved from natural coronafacic acid

(+)-(2) and coronamic acid (+)-(3), which was obtained by synthesis and optical resolution.^{2b)} More recently, many different syntheses of ($\pm$)-2 have been reported by several groups³⁾; however, there has been no approach to optically-active coronafacic acid. In this communication, we describe the synthesis of (+)- and (-)-2 via the chromatographic resolution of the *l*-menthyl ester derivative, which was prepared as a synthetic intermediate by the modification of our previous work.^{3c)}

In our synthesis of racemic 2,^{3c)} the C₆-ethyl group had been introduced by alkylation of a tricyclo[4.3.0.0^{1,5}]nonane derivative, producing a significant amount of the dialkylation by-product. To circumvent the trouble in this investigation, *l*-menthyl 3-oxohexanoate (4) ([α]_D²⁰ -63.5° (*c*=0.85, CHCl₃); MS *m/z*: 268 (M⁺)) was prepared by the reaction of the dianion of *l*-menthyl acetoacetate⁴⁾ and ethyl

bromide in an 88% yield. Deprotonation of **4** with sodium hydride and *n*-butyl lithium, followed by treatment with 1-cyclopentenylmethyl *p*-toluenesulfonate (**5**),^{3c)} afforded a 75% yield of a β -keto ester (**6**) (MS *m/z*: 348 (M^+); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1735, 1710, 1645, 1305; NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CCl}_4}$: 3.27 (2H, s), 4.67 (1H, m), 5.35 (1H, bs)). Diazotization of **6** and subsequent intramolecular carbenoid addition^{3c)} gave a mixture of the desired diastereomers (**7**), in which the C_6 -ethyl group is *trans* to the C_{3a} -proton, and their isomers (**8**) in a 56% yield. Treatment of these with sodium methoxide in refluxing methanol caused the epimerization of **8** to give only **7** as a 1:1 diastereomeric mixture, which was resolved cleanly by chromatography on silica gel (EtOAc–hexane) and recrystallization (methanol).

The more polar diastereomer of **7** (mp $70 \sim 71^\circ\text{C}$; $[\alpha]_{\text{D}}^{20} - 86.7^\circ$ ($c = 4.65$, CHCl_3); MS *m/z*: 346 (M^+); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 1740, 1720, 1220) was reduced with zinc borohydride to give a 90% yield of a hydroxy ester (**9**) ($[\alpha]_{\text{D}}^{20} - 67.5^\circ$ ($c = 1.53$, CHCl_3); MS *m/z*: 330 ($M^+ - 18$); IR $\nu_{\text{max}}^{\text{CHCl}_3}$ cm^{-1} : 3600, 1710, 1225; NMR $\delta_{\text{Me}_4\text{Si}}^{\text{CCl}_4}$: 4.05 (1H, d, $J = 6.5$)). To ensure the hydrolysis in the last step,^{*1} **9** was converted into a methyl ester (**10**) ($[\alpha]_{\text{D}}^{20} - 43.5^\circ$ ($c = 1.82$, CHCl_3); MS *m/z*: 224 (M^+)) in an 88% yield by hydrolysis with refluxing aqueous sodium hydroxide in DMSO, followed by esterification with diazomethane. Treatment of **10** with *p*-toluenesulfonyl chloride in pyridine gave an unseparable mixture (1:1:1; glc analysis) of α,β -unsaturated esters (**11**). The mixture was directly subjected to hydroboration and subsequent oxidation with pyridinium chlorochromate to give a complex mixture, from which a keto ester (**12**) ($[\alpha]_{\text{D}}^{20} + 83.7^\circ$ ($c = 1.99$, CHCl_3); MS *m/z*: 222 (M^+)) was obtained in an 8% yield from **10** by preparative TLC. Hydrolysis of **12** with aqueous hydrochloric acid gave (+)-**2** (mp $142 \sim 143^\circ\text{C}$; $[\alpha]_{\text{D}}^{20}$

$+ 109^\circ$ ($c = 0.75$, MeOH), lit.^{1a)} mp $125 \sim 126^\circ\text{C}$; $[\alpha]_{\text{D}}^{20} + 119.1^\circ$, natural sample*²: mp $142 \sim 143^\circ\text{C}$; mmp $142 \sim 143^\circ\text{C}$), whose spectral and analytical data, as well as the sign of the optical rotation, were identical with those of the natural product. Similarly, (–)-**2** (mp $142 \sim 143^\circ\text{C}$; $[\alpha]_{\text{D}}^{20} - 119^\circ$ ($c = 0.86$, MeOH)) was obtained from the less polar diastereomer of **7** (mp $100 \sim 101.5^\circ\text{C}$; $[\alpha]_{\text{D}}^{20} + 5.4^\circ$ ($c = 3.68$, CHCl_3)); thus the absolute configurations of **7** became clear, namely the more polar one must have the structure (**7a**) and the less polar one (**7b**).

As the result, the formal total synthesis of optically-active coronatine was completed.

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*1 Hydrolysis of **7** or the *l*-menthyl ester of **2** was unsuccessful under several conditions tried.

*2 The characteristics of natural coronafacic acid were measured in this laboratory.