Short Communication

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

Mitsuru Nakayama and Susumu Ohira

Department of Chemistry, Faculty of Science, Hiroshima University, Higashisenda-machi, Naka-ku, Hiroshima 730, Japan

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Coronatine (1), a phytotoxin produced by Pseudomonas coronafaciens var. atropurpurea, induces chlorosis on the leaves of Italian ryegrass 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 (±)-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[4.3.0.0¹5]nonane derivative, producing a significant amount of the dialkylation by-product. To circumvent the trouble in this investigation, l-menthyl 3-oxohexanoate (4) ([α]D 20° = −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), afforded a 75% yield of a β-keto ester (6) (MS m/z: 348 (M⁺); IR ν\text{CHCl₃} cm⁻¹: 1735, 1710, 1645, 1305; NMR δ\text{MeSi} ppm: 3.27 (2H, s), 4.67 (1H, m), 5.35 (1H, bs)). Diazotization of 6 and subsequent intramolecular carbenoid addition gave a mixture of the desired diastereomers (7), in which the C₆-ethyl group is trans to the C₃α-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 ~ 71°C; [α]D²⁰ -86.7° (c=4.65, CHCl₃); MS m/z: 346 (M⁺); IR ν\text{CHCl₃} cm⁻¹: 1740, 1720, 1220) was reduced with zinc borohydride to give a 90% yield of a hydroxy ester (9) ([α]D²⁰ -67.5° (c=1.53, CHCl₃); MS m/z: 330 (M⁺ - 18); IR ν\text{CHCl₃} cm⁻¹: 3600, 1710, 1225; NMR δ\text{MeSi} ppm: 4.05 (1H, d, J=6.5)). To ensure the hydrolysis in the last step, 9 was converted into a methyl ester (10) ([α]D²⁰ -43.5° (c=1.82, CHCl₃); 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 unsoluble mixture (1:1:1; gc 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) ([α]D²⁰ +83.7° (c=1.99, CHCl₃); 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 ~ 143°C; [α]D²⁰ +109° (c=0.75, MeOH), lit.¹ mp 125 ~ 126°C; [α]D²⁰ +119.1°, natural sample² mp 142 ~ 143°C; mmp 142 ~ 143°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 ~ 143°C; [α]D²⁰ -119° (c=0.86, MeOH)) was obtained from the less polar diastereomer of 7 (mp 100 ~ 101.5°C; [α]D²⁰ + 5.4° (c=3.68, CHCl₃)); 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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REFERENCES


*¹ Hydrolysis of 7 or the l-methyl ester of 2 was unsuccessful under several conditions tried.
*² The characteristics of natural coronafacic acid were measured in this laboratory.