Short Communication

Asymmetric Total Syntheses of (+)-Coronafacic Acid and (+)-Coronatine

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An asymmetric total synthesis of (+)-coronafacic acid, starting from (R)-(−)-4-acetoxy-2-cyclopentanone as a chiral source, was accomplished. Construction of the 1-hydrindanone framework was carried out by using intramolecular 1,6-conjugate addition as the key step. Coupling between (+)-coronafacic acid and protected coronaminic acid, and subsequent deprotection provided (+)-coronatine. This is the first asymmetric total synthesis of (+)-coronatine.

Key words: coronafacic acid; coronatine; coronaminic acid; asymmetric synthesis; 1,6-conjugate addition

The phytotoxins, coronatine (1) and coronafacic acid (2), have been isolated from a culture broth of Pseudomonas syringae pv. atropurpurea as a cholorosis-inducing factor on the leaves of Italian ryegrass.11 There has been strong recent interest in 1 and 2 which have been shown to exhibit various biological activities similar to those of jasmonic acid (4), which is known as an endogenous plant-growth regulator and signal transmitter.2) It was suggested that the structural similarity among 1, 2, and 4, particularly around their cyclopentane rings and including the stereogenic centers, would result in their exhibiting the same activities.

In order to supply a sufficient amount of 1, an efficient synthetic approach is urgently needed, because 1 can rarely be obtained from the culture broth. Previous syntheses of 2 have not always been satisfactory in their efficiency.3) Moreover, there is only one example leading to the synthesis of optically active 2.3a) In this paper, we describe asymmetric total syntheses of (+)-2 and (+)-1 via our new approach.

We have recently reported the total synthesis of racemic 2 by using intramolecular 1,6-conjugate addition as the key step.4) In principle, our route is applicable to the synthesis of optically active 2; therefore, preparation of optically active ester 8 would be most important (Scheme). (R)-(−)-4-Acetoxy-2-cyclopentanone (5; >99% e.e.)31 was used as a chiral source and converted into 6 in 63% yield by using the chirality transfer method reported by Grebe et al.7) Deallylation of 6 with the palladium catalyst system and subsequent decarboxylation both proceeded smoothly. The resulting tert-butyl ester was hydrolyzed in formic acid to give carboxylic acid 7 in a 45% yield (2 steps before being recrystallized twice). Esterification of 7 with ethyl iodide and sodium hydrogen carbonate gave an ethyl ester (91%), which was hydrogenated in the presence of 10% palladium on carbon (Pd-C) to give a saturated keto-ester. Acetaliza-

![Diagram of structures and synthesis](image-url)
tion of the carbonyl group with ethylene glycol and pyridinium p-toluenesulfonate gave desired ester 8 (85%, 2 steps, 96% e.e.).

Optically active ester 8 was converted into the precursor for intramolecular 1,6-conjugate addition, (E)-α,β,γ,δ-unsaturated ester 9 as the sole product in a 68% yield (4 steps), by following the synthetic route for racemic 2: (1) aldol condensation between the lithium enolate of 8 and 2-ethylcyclohexene; (2) mesylation with mesyl chloride and 4-dimethylaminopyridine; (3) elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); (4) decarboxylation with p-toluenesulfonic acid in acetone. Treatment of 9 with sodium ethoxide in ethanol gave 10a (96% e.e) and its C0-epimer 10b in a 70% yield (diastereoselectivity; 10a : 10b = 3 : 1, which were readily separable by medium-pressure column chromatography). These results demonstrate that 10a could be synthesized in a 53% yield in an one-step reaction, and the optical purity of 8 could be completely retained through a sequence of reactions including intramolecular 1,6-conjugate addition. Furthermore, 10b could be isomerized to 10a with DBU in refluxing benzene (10a : 10b = 1 : 1). Acidic hydrolysis of 10a gave (+)-2 in a 95% yield; mp 141–142°C, [α]D20 +106° (c 1.00, MeOH) [lit. mp 141–142°C, [α]D20 +119° (c 3.30, MeOH)].9,10 whose spectral data were identical with those of natural 2 in all respects. The optical purity of (+)-2 was estimated to be at least >96% e.e. based on that of 10a.

We had already developed a practical stereoselective synthesis for (+)-coronamic acid (3) and obtained protected amino acid 11,11 which would be considered a useful substrate for amide formation. After deprotection of the Boc group of 11 with trifluoroacetic acid (TFA), the resulting amine TFA salt was coupled with (+)-2 in the presence of a water-soluble carbodiimide to give 12 in an 88% yield. In a preliminary experiment, coupling between racemic 2 and deprotected 11 gave a mixture of desired compound 12 and its diastereomer (inseparable on TLC), whose 1H-NMR spectrum gave partially separated signals based on the respective diastereomer (ratio ca. 1 : 1). However, in the case of coupling (+)-2, the 1H-NMR spectrum of 12 was observed as a single diastereomer. This result means that (+)-2 had practically enantiomeric purity and that 12 can be regarded as optically pure. Deprotection of 12 by hydrogenolysis in the presence of 10% Pd–C in ethyl acetate provided (+)-1 in an 80% yield; mp 162–164°C, [α]D20 +76.6° (c 2.20, MeOH) [mp 161–163°C, [α]D20 +68.4° (c 2.20, MeOH)].1a,11 The spectral data for synthetic (+)-1 were identical with those of natural 1 in all respects including the specific rotation. In this way, the first asymmetric total synthesis of (+)-1 (44%, 2 steps from natural 2).

In conclusion, the asymmetric total synthesis of (+)-2 has been completed via the intramolecular 1,6-conjugate addition approach, and (+)-2 has been converted into optically pure (+)-1 via the coupling with 11. Our synthesis makes it possible to supply a practical amount of (+)-1, which is the most valuable probe at the present stage in the area of plant physiological studies relating to 4. A study of structure-activity relationships by using the analogs of 1 and the biosynthetic precursors of 4 is also in progress.

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References and Notes


6) Satisfactory spectroscopic data were obtained for all the new compounds.


8) Column, Chiralcel OC® (64.6 x 250 mm); eluent, hexane/2-propanol (96/4); flow rate, 0.3 ml/min; detection, UV 220 nm; retention times: 8, 36 min; enantiomer of 8, 40 min.

9) The same column and conditions as those in ref. 8 were used; detection by UV at 240 nm retention times: 10a, 64 min; 10b, 59 min.

10) Although the first reported mp of natural (+)-2 is described as 125–126°C in ref. 1a, the corrected mp value is described as 141–142°C in the thesis of Dr. K. Shiraishi (Hokkaido University, 1978). Furthermore, Prof. M. Nakayama has reported mp 142–143°C for his synthetic (+)-2 ([α]D20 +109°) and our natural sample in ref. 3a.


12) Although the mp of natural (+)-1 is described as 151–153°C in ref. 1a, 161–163°C is the corrected value in the thesis of Dr. K. Shiraishi. Since we have no natural sample at the present time, the specific rotations, which may be influenced by the temperature, cannot be compared directly.