Biosci. Biotech. Biochem., **61** (4), 752–753, 1997

Short Communication

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

Hiroaki TOSHIMA, Shinji NARA, and Akitami ICHIHARA

Department of Bioscience and Chemistry, Faculty of Agriculture, Hokkaido University, Sapporo 060, Japan

Received December 6, 1996

An asymmetric total synthesis of (+)-coronafacic acid, starting from (*R*)-(+)-4-acetoxy-2-cyclopen-1-one 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 coronamic acid, and subsequent deprotection provided (+)-coronatine. This is the first asymmetric total synthesis of (+)-coronatine.

Key words: coronafacic acid; coronatine; coronamic 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 chlorosis-inducing factor on the leaves of Italian ryegrass.[1] 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 cyclopentanone 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-cyclopen-1-one (**5**; >99% *e.e.*)[5] was used as a chiral source and converted into **6**[6] in a 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-

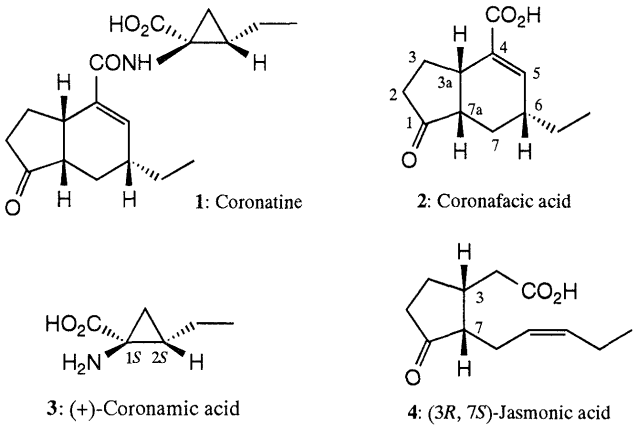
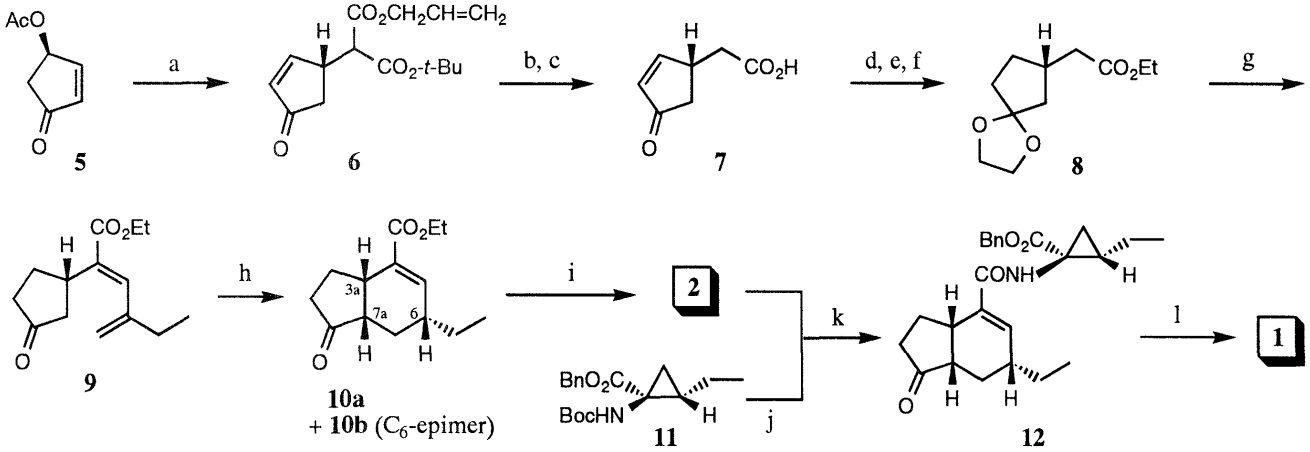


Fig. Structures of Coronatine and the Related Compounds.



(a) allyl *t*-butyl malonate, K_2CO_3, 18-crown-6 / toluene, 63% (b) $Pd(OAc)_2$, PhP_3, HCO_2H, Et_3N / 1, 4-dioxane (c) HCO_2H, 45%, 2 steps after recrystallization (d) $NaHCO_3$, EtI / DMF, 91% (e) H_2, 10% Pd-C / EtOH (f) PPTS, ethylene glycol / benzene, 85%, 2 steps (g) see ref. 4, 68%, 4 steps (h) NaOEt / EtOH, 70%, **10a** : **10b** = 3:1 (i) 3 N HCl, 95% (j) TFA / CH_2Cl_2, then evaporation, 100% (k) $EtN{=}C{=}N(CH_2)_3NMe_2{\cdot}HCl$, Et_3N, DMAP / CH_2Cl_2, 88% (l) H_2, 10% Pd-C / EtOAc, 80%

Scheme

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

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-ethylacrolein; (2) mesylation with mesyl chloride and 4-dimethylaminopyridine; (3) elimination with 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); (4) deacetalization with *p*-toluenesulfonic acid in acetone.[4] Treatment of **9** with sodium ethoxide in ethanol gave **10a** (96% *e.e*)[9] and its C_6-epimer **10b** in a 70% yield (diastereoselectivity; **10a** : **10b** = 3 : 1, which were readily separable by medium-pressure columun 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, $[\alpha]_D^{23}$ +106° (*c* 1.00, MeOH) [lit. mp 141–142°C, $[\alpha]_D^{20}$ +119° (*c* 3.30, MeOH)],[1a,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 deprotecting 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 ^{1}H-NMR spectrum gave partially separated signals based on the respective diastereomer (ratio *ca.* 1 : 1). However, in the case of coupling (+)-**2**, the ^{1}H-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, $[\alpha]_D^{22}$ +76.6° (*c* 2.20, MeOH) [mp 161–163°C, $[\alpha]_D^{20}$ +68.4° (*c* 2.20, MeOH)].[1a,12] 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** was completed. The yield (70%, 2 steps from **2**) was remarkably improved, in contrast to the previous partial 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.

Acknowledgments. We are grateful to Mr. K. Watanabe and Dr. E. Fukushi in our faculty for measuring the MS spectra.

References and Notes

1) (a) A. Ichihara, K. Shiraishi, H. Sato, S. Sakamura, K. Nishiyama, R. Sakai, A. Furusaki, and T. Matsumoto, *J. Am. Chem. Soc.*, **99**, 636–637 (1977); (b) A. Ichihara, K. Shiraishi, S. Sakamura, K. Nishiyama, and R. Sakai, *Tetrahedron Lett.*, **1977**, 269–272; (c) A. Ichihara, K. Shiraishi, S. Sakamura, A. Furusaki, N. Hashimoto, and T. Matsumoto, *Tetrahedron Lett.*, **1979**, 365–368.

2) (a) F. Greulich, T. Yoshihara, and A. Ichihara, *J. Plant Physiol.*, **147**, 359–366 (1995); (b) T. Krumm and W. Boland, *Molecules*, **1**, 23–26 (1996); (c) Y. Koda, K. Takahashi, Y. Kikuta, F. Greulich, H. Toshima, and A. Ichihara, *Phytochemistry*, **41**, 93–96 (1996) and references cited therein.

3) (a) M. Nakayama and S. Ohira, *Agric. Biol. Chem.*, **47**, 1689–1690 (1983); (b) G. Mehta and M. Pravean, *J. Chem. Soc., Chem. Commun.*, **1993**, 1573–1575 and references cited therein; (c) S. Holder and S. Blechert, *Synlett*, **1996**, 505–506.

4) S. Nara, H. Toshima, and A. Ichihara, *Tetrahedron Lett.*, **37**, 6745–6748 (1996).

5) (a) D. R. Deardorff, A. J. Matthews, D. S. McMeekin, and C. L. Craney, *Tetrahedron Lett.*, **27**, 1255–1256 (1986); (b) A. G. Myers, M. Hammond, and Y. Wu, *Tetrahedron Lett.*, **37**, 3083–3086 (1986) and references cited therein.

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

7) H. Grebe, A. Lange, H. Riechers, K. Kieslich, W. Viergutz, P. Washausen, and E. Winterfelt, *J. Chem. Soc., Perkin Trans. 1*, **1991**, 2651–2655.

8) Column, Chiralcel OC® (φ4.6 × 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** ($[\alpha]_D^{20}$ +109°) and our natural sample in ref. 3a.

11) H. Toshima and A. Ichihara, *Biosci. Biotech. Biochem.*, **59**, 495–500 (1995).

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.