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Asymmetric Total Syntheses of (+)-Coronafacic Acid and (+)-Coronatine, Phytotoxins Isolated from *Pseudomonas Syringae* Pathovars

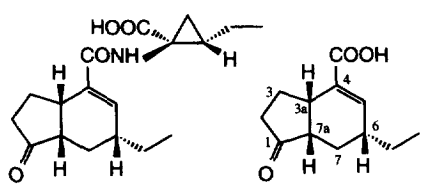
Shinji Nara, Hiroaki Toshima,* and Akitami Ichihara*

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

Abstract: Asymmetric total synthesis of (+)-coronafacic acid (**2**), was accomplished *via* intramolecular 1, 6-conjugate addition as the key step. The chiral ester (+)-**7** was prepared *via* two approaches: starting from (*R*)-(+)-4-acetoxy-2-cyclopenten-1-one (**12**), and using catalytic asymmetric Michael reactions promoted by heterobimetallic BINOL complexes. Coupling between (+)-**2** and the protected coronamic acid **8** and subsequent deprotection by hydrogenolysis provided (+)-coronatine (**1**). This is the first asymmetric total synthesis of (+)-**1**. © 1997 Elsevier Science Ltd.

INTRODUCTION

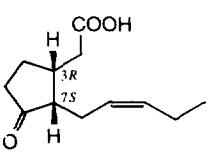
The phytotoxins, coronatine (**1**) and coronafacic acid (**2**), have been isolated from a culture broth of *Pseudomonas syringae* pv. *atropurpurea* as chlorosis-inducing factors on the leaves of Italian ryegrass.[1] An amide compound **1** is made up from **2** as the acid component and coronamic acid (**3**) as the amine component, which has not been usually found as a free amino acid in a culture broth.[2] Several pathovars of *Pseudomonas syringae*'(pv. *maculicola*, pv. *morsprunorum*, pv. *glycinea*, and pv. *tomato*) and *Xanthomonas compestris* pv. *phormiicola* also produce **1** along with the analogues possessing different amino acid components (norcoronamic acid, L-isoleucine, L-alloisoleucine, and L-valine).[3]



Coronatine (**1**)

Coronafacic acid (**2**)

Coronamic acid (**3**)

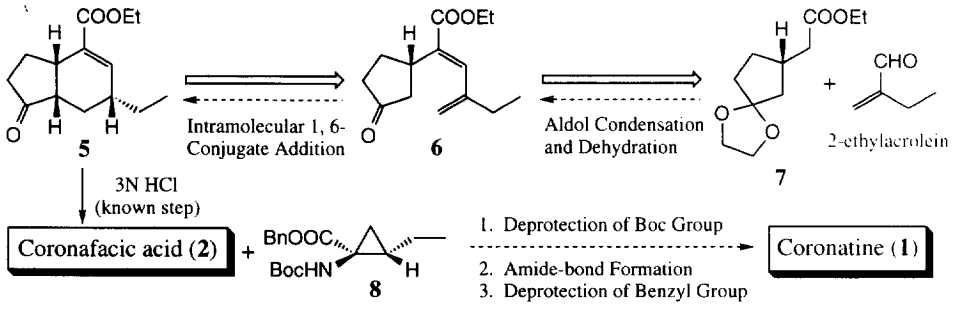


(3*R*, 7*S*)-Jasmonic acid (**4**)

Recently, there has been much interest in **1** which has been shown to exhibit various biological activities similar to those of (3*R*, 7*S*)-jasmonic acid (**4**), known as an endogenous plant-growth regulator and signal transmitter.[4] Furthermore, the potent activities of **1** (for example, *in vitro*: potato tuber-inducing activity, 10^{-10}

M ; potato cell expansion-inducing activity, 10^{-8} M) are 100 to 10,000 times higher than those of **4**. Coronafacic acid **2** itself also exhibits equal or slightly weaker activities of **4** in some bioassay systems.[4] It is suggested that the structural similarity among **1**, **2**, and **4**, particularly around their cyclopentanone ring parts including the stereogenic centers, would result in exhibiting the same activities. The bicyclic structure of **1** and **2** contributes to the retention of the C_{3a} and C_{7a} stereogenic centers as *cis*-relationship; however, the monocyclic compound **4** readily undergoes isomerization at the C_7 position *via* enolization to provide *trans*-isomer, (3*R*, 7*R*)-jasmonic acid. In addition to the *cis*-relationship in the cyclopentanone ring parts, undoubtedly, the presence of the coronamic acid part in **1** influences significantly the exhibiting of biological activities. Therefore, **1** and **2**, themselves or as lead compounds, would play important roles in the area of plant physiological study relating to **4**.

In order to supply a sufficient amount of **1**, an efficient synthetic approach is urgently needed, because **1** can rarely be obtained from culture broths of *Ps. syringae* pathovars. Even under our optimum conditions, only 0.24 mg of **1** was isolated from one liter of culture broth. Moreover, the large-scale culture caused decrease of the yield. Although several syntheses of racemic **2**, in connection with the methodology on constructing the hydrindane framework, have been previously reported,[5] they are not always satisfactorily efficient. Moreover, there is only one example, reported by Nakayama *et al.*, leading to the synthesis of the optically active **2**.[5g] We have reported the partial synthesis of **1** by coupling between the acid chloride derived from natural **2** and the synthetic (+)-**3** as free amino acid in the presence of magnesium oxide; however, the yield was low.[1b] In this paper, we describe in detail the asymmetric total synthesis of (+)-**2** and (+)-**1** *via* our new approach.[6]



Scheme 1

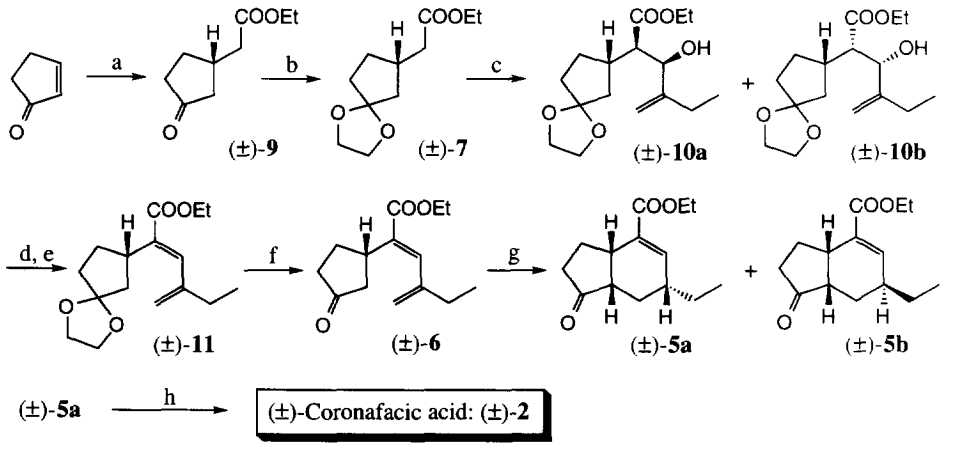
Our synthetic strategy is shown in Scheme 1. The key step is one-step construction of the 1-hydrindanone framework possessing the desired functional groups and stereogenic centers by using 1, 6-conjugate addition. Therefore, the ethyl ester **5** of coronafacic acid is retrosynthesized to α, β, γ, δ-unsaturated ester **6** and further to cyclopentanone derivative **7** and 2-ethylacrolein. Aldol condensation between **7** and 2-ethylacrolein, and subsequent dehydration would provide **6**. Intramolecular 1, 6-conjugate addition of **6** would provide **5** and the stereogenic centers (C_6, C_{7a}) would be favorably controlled at this stage. This stereocontrol is based upon the originally existing C_{3a} stereogenic center. Intramolecular 1, 6-conjugate addition would proceed in *cis*-mode to provide the *cis*-hydrindane framework, and subsquent protonation of the resulting dienolate would occur from the convex face to provide **5**. Therefore, in principle, this route is applicable to the synthesis of the optically active **2** by using the chiral **7** as the starting material. Practical stereoselective synthesis of (+)-coronamic acid

(**3**) has already been completed, and the intermediate **8**[7] would be useful for amide-bond formation leading to total synthesis of **1**.

RESULTS AND DISCUSSION

Total Synthesis of (±)-Coronafacic Acid

We examined the possibility of intramolecular 1, 6-conjugate addition, our new approach for construction of the 1-hydrindanone framework of **2**,[6a] on a racemic substrate prior to on an optically active one. 2-Cyclopenten-1-one was converted to the known ester (±)-**9**[8] with magnesium monoethyl malonate *via* malonic ester synthesis (Scheme 2). The carbonyl group of (±)-**9** was protected with ethyleneglycol as cyclic acetal to give (±)-**7** in 89% yield. Aldol condensation was achieved between the lithium enolate of (±)-**7** and 2-ethylacrolein, and diastereomeric hydroxy esters (±)-**10a** and (±)-**10b** possessing *syn*-relationship were selectively obtained in 92% yield. Since the relative stereochemistry between the ethoxycarbonyl group and the hydroxyl group could not be determined at this stage, the mixture was further converted to α, β, γ, δ-unsaturated ester by the conventional method. Mesylation of the hydroxyl group and subsequent elimination with DBU provided (*E*)-isomer (±)-**11** as the sole product in 83% yield (2 steps). ^{1}H-^{1}H-NOE experiment revealed that (±)-**11** possesses (*E*)-geometry and *s-cis* conformation, which were considered to be favorable for the next cyclization.[9] Thus, the *syn*-relationship between the ethoxycarbonyl group and the hydroxyl group in (±)-**10a** and (±)-**10b** was proved by the transformation to (±)-**11**.[6a] High stereoselectivity of this aldol condensation was caused by stereoselective formation of (*E*)-enolate of (±)-**7** and by contribution of the alkenyl moiety of 2-ethylacrolein as steric hindrance in the transition state.[10] Deacetalization of (±)-**11** with *p*-TsOH in acetone gave ketone (±)-**6**, which was presented in the retrosynthesis (Scheme 1). Thus, the requisite precursor for intramolecular 1, 6-conjugate addition was set up.



(a) ref. 8 (b) *p*-TsOH, ethyleneglycol / benzene, reflux, 89% (c) LDA / THF, then 2-ethylacrolein, 92% (d) MsCl, DMAP / CH_2Cl_2 (e) DBU / CH_2Cl_2, 83%, 2 steps (f) *p*-TsOH / acetone, 99% (g) NaOEt (3 eq.) / EtOH, 71%, **5a** : **5b** = 3 : 1 (h) 3N HCl, reflux, 95%

Scheme 2

Intramolecular 1, 6-conjugate addition was carried out under some basic conditions. α, β-Unsaturated esters and / or γ, δ-unsaturated ester were obtained depending on conditions. When pyrrolidine was used as a base, an enamine generated *in situ* might play the role of donor. Of course, an enolate anion acts as the donor in the case of using alkaline metal alkoxide. Among several attempted conditions, our purpose, one-step construction of a 1-hydrindanone framework possessing the desired functional groups and stereogenic centers, was accomplished in the case of using EtONa (3.0 eq.) / EtOH. Under this condition, only α, β-unsaturated esters (±)-**5a** and (±)-**5b** (separable by using a Lobar® column) were obtained in 3:1 ratio and in 71% yield. This result demonstrates that the desired compound (±)-**5a**, possessing the three desired stereogenic centers (C_{3a}, C_{7a}, C_6), could be synthesized in one step (53% yield) *via* intramolecular 1, 6-conjugate addition. Since the same diastereoselectivitiy was observed in the case of using EtOLi and EtOK instead of EtONa, the counter cations would not influence the diastereoselectivitiy. Although prolongation of the reaction time resulted in decreasing the diastereoselectivity [up to (±)-**5a** : (±)-**5b** = *ca.* 1:1], (±)-**5b** could be isomerized to (±)-**5a** with DBU in refluxing benzene [up to (±)-**5a** : (±)-**5b** = *ca.* 1:1]. Studies to elucidate the reaction mechanism and to increase the diastereoselectivity are under way.

Acidic hydrolysis (3N HCl, reflux) of (±)-**5a** provided (±)-coronafacic acid; (±)-**2** (mp 125-128℃, lit.[5a] mp 117-119℃) in 70% yield, whose spectral data were identical with those of the natural product in all respects. Particularly, the ^{1}H-NMR spectrum of synthetic (±)-**2** was completely identical with that of natural **2** with a 270 MHz NMR-spectrometer. In our first report in 1977[1a], all proton signals of **2** could not be assigned with a 90 MHz NMR-spectrometer, and the characteristic signal (δ 3.15 ppm, 1H, quintet-like shape) appearing apart from others was estimated as the C_{7a}-H due to deshielding by the carbonyl group. However, the full assignment of all proton signals was achieved by using ^{1}H-^{1}H-COSY spectrum with a high field NMR-spectrometer (500 MHz). The result reveals that the signals at δ 2.37 ppm and δ 3.08 ppm (corresponding to δ 3.15 ppm in the previous study) are assigned as the C_{7a}-H and C_{3a}-H, respectively. In this way, an efficient total synthesis of **2** has been accomplished by using the intramolecular 1, 6-conjugate addition as the key step. The overall yield by our new route, which was improved remarkably in contrast to those of previous syntheses, was 24% in 8 steps from 2-cyclopenten-1-one, a commercially available starting material.

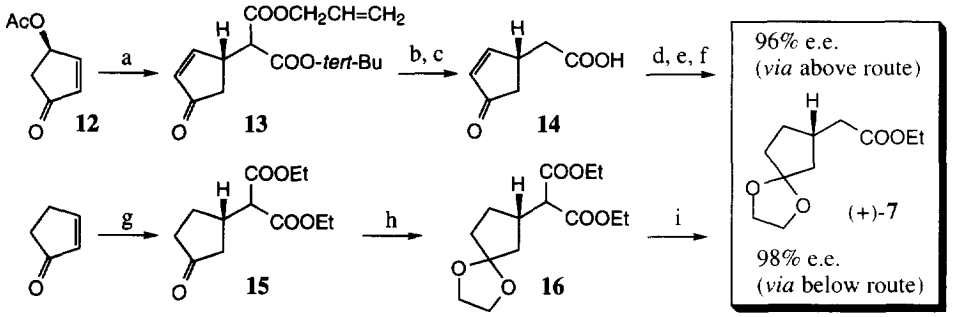
Total Synthesis of (+)-Coronafacic Acid

The preparation of the optically active ester **8** is the main objective in the total synthesis of (+)-**2**. Two approaches, starting from a chiral and an achiral compound were achieved (Scheme 3).

In the first approach, (*R*)-(+)-4-acetoxy-2-cyclopenten-1-one (**12**),[11] whose preparation is well established in the area of the prostanoid and related chemistry, was used as a chiral source in order to introduce the asymmetry of the C_{3a}-position in **2**. The chiral enone **12** was converted into **13** in 74% yield by using the chirality transfer method reported by Grebe *et al.*[12] Although *tert*-butyl methyl malonate (commercially available) was originally used, on the whole, allyl *tert*-butyl malonate (prepared from *tert*-butyl methyl malonate) gave better results from the viewpoint of facility in subsquent functionalizations. Deallylation of **13** with the palladium catalyst system and subsequent decarboxylation both proceeded smoothly in one pot. The resulting *tert*-butyl ester was hydrolyzed in formic acid to give crystalline carboxylic acid **14** in 45% yield (2 steps before being recrystallized twice). Therefore, the finding of optimized recrystallization conditions would provide the optically pure **14**. Esterification of **14** with ethyl iodide and sodium hydrogen carbonate gave an ethyl ester in 91% yield, which was hydrogenated in the presence of 10% Pd-C to give a saturated keto ester derivative.

Acetalization of the carbonyl group with ethyleneglycol and PPTS gave the desired ester (+)-**7** in 85% yield (2 steps). The optical purity of (+)-**7** was determined as 96% e.e. by an HPLC analysis using a chiral column.[13] As mentioned above, recrystallization of **14** was required to increase the optical purity, which might be decreased in a Michael reaction (chirality transfer method). Actually, 92% e.e. of (+)-**7** was obtained from nearly 100% e.e. of **12**, when **14** was not recrystallized. Decrease of the optical purity and a moderate yield based on the production of a di-adduct, are disadvantages in the early stage. Therefore, a Michael reaction using allyl ethyl malonate, whose preparation requires further steps, was not attempted.

The second approach was examined to provide (+)-**7** more efficiently. The catalytic asymmetric Michael reaction promoted by heterobimetallic BINOL complexes, developed by Shibasaki and co-workers,[14] is considered to be the best method to fill our requirement from both points of yield and optical purity. As used in the synthesis of (±)-**2**, 2-cyclopenten-1-one is again used as the starting material. Diethyl malonate was chosen as the donor, because we used the ethyl esters in the synthesis of racemic **2**. By using several combinations of catalysts and additives, catalytic asymmetric Michael reactions between 2-cyclopenten-1-one and diethyl malonate were examined. By using the combination of a Ga-Na-(*S*)-BINOL complex (10 mol %) with sodium *tert*-butoxide (7 mol %),[14c] **15** was obtained in a practical scale (4.6 g) and in 95% yield. The optical purity of **15** was determined after two-step conversion to (+)-**7**. Acetalization of **15** with *p*-TsOH and 2-ethyl-2-methyl-1, 3-dioxolane gave **16** in 88% yield. Conversion of **16** into a half-acid and subsequent decarboxylation proceeded smoothly in one-pot under neutral conditions (LiCl / DMSO) to give (+)-**7** in 84% yield. The optical purity of (+)-**7** was determined as 98% e.e.,[13] which was a sufficient value for the syntheses of optically pure (+)-**2** and (+)-**1**. In this way, the preparation of optically active ester (+)-**7** was efficiently improved; 70% overall yield in 3 steps and 98% e.e. without increasing the optical purity by recrystallization.

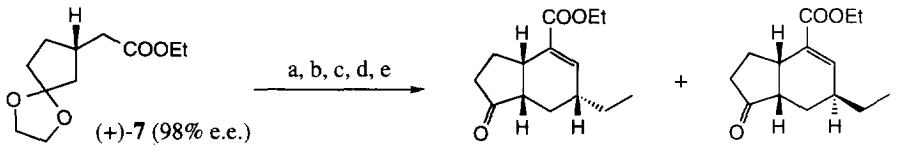


(a) allyl *t*-butyl malonate, K_2CO_3, 18-crown-6 / toluene, 74% (b) $Pd(OAc)_2$, Ph_3P, HCO_2H, Et_3N / 1, 4-dioxane (c) HCO_2H, 45%, 2 steps (d) $NaHCO_3$, EtI / DMF, 91% (e) H_2, 10% Pd-C / EtOH (f) PPTS, ethyleneglycol / benzene, reflux, 85%, 2 steps (g) diethyl malonate, Ga-Na-(*S*)-BINOL complex (10 mol %), *t*-BuONa (7 mol %) / THF-Et_2O, 95% (h) *p*-TsOH / 2-ethyl-2-methyl-1, 3-dioxolane, ethyleneglycol, 88% (i) LiCl / DMSO, 84%

Scheme 3

The total synthesis of (+)-**2** was carried out by following the synthetic route of racemic **2**[6a] (Scheme 4 and also see Scheme 2). Aldol condensation between the lithium enolate of (+)-**7** (98% e.e) and 2-ethylacrolein proceeded stereospecifically in the newly-formed stereogenic centers to give a *ca.* 1:1 mixture of **10a** and **10b**

(optically active), which possesses a *syn*-relationship between the ethoxycarbonyl and hydroxyl groups. Mesylation of the mixture of **10a** and **10b** and subsequent β-elimination with DBU gave α, β, γ, δ-unsaturated ester (-)-**11** possessing (*E*)-geometry as the sole product in 90% yield [3 steps from (+)-**7**]. Deacetalization of (-)-**11** with *p*-TsOH in acetone gave (-)-**6**, the precursor of intramolecular 1, 6-conjugate addition in 94% yield. Treatment of (-)-**6** with NaOEt (3 eq.) in EtOH gave (+)-**5a** corresponding to the ethyl ester of coronafacic acid and its C_6-epimer (+)-**5b** in 76% yield (diastereoselectivity; *ca.* 3:1). The optical purity of (+)-**5a** was determined as 98% e.e.by an HPLC analysis using a chiral column.[15] This result demonstrates that the optical purity of (+)-**7** was completely retained in (+)-**5a** without any loss through the sequence of reactions including intramolecular 1, 6-conjugate addition. In a preliminary communication, we described that 96% e.e. of (+)-**7** was also converted to 96% e.e. of (+)-**5**.[6b] The effectiveness of our new approach, on both racemic and optically, active forms, was proved. Acidic hydrolysis of (+)-**5a**[16] gave (+)-**2** in 70% yield after recrystallization; mp 142-143℃; $[\alpha]_D^{23}$ +122° (*c* 1.00, MeOH) [lit. mp 141-142℃; $[\alpha]_D^{20}$ +119° (*c* 3.30, MeOH)],[1a,17] whose spectral data were identical with those of natural **2** in all respects. The overall yield *via* our new route was 24% in 9 steps from 2-cyclopenten-1-one. The optical purity of (+)-**2** is estimated at least >98% e.e. based on 98% e.e. of (+)-**5a**. In practice, judging from the specific rotation, (+)-**2** can be regarded as opptically pure.



(+)-**5a** $\xrightarrow{f}$ (+)-Coronafacic acid: (+)-**2** [mp 142-143 °C; $[\alpha]_D^{23}$ +122° (*c* 1.00, MeOH); lit. mp 141-142 °C; $[\alpha]_D^{20}$ +119° (*c* 3.30, MeOH)]

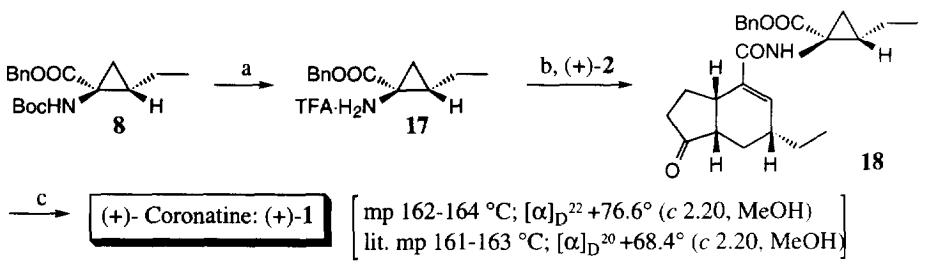
(a) LDA / THF, then 2-ethylacrolein (b) MsCl, DMAP / CH_2Cl_2 (c) DBU / CH_2Cl_2, 90% , 3 steps (d) *p*-TsOH / acetone, 94% (e) NaOEt (3 eq.) / EtOH, 76%, **5a** : **5b** = 3 : 1 (f) 3N HCl, reflux, 70%

Scheme 4

Total Synthesis of (+)-Coronatine

The final objective of our project is the total synthesis of (+)-**1**. The practical stereoselective synthesis of (+)-coronamic acid (**3**), *via* cyclopropanation between the chiral cyclic sulfate derived from (*R*)-malic acid and dibenzyl malonate, and subsquent diastereoselective hydrolysis as the key steps, has been already developed.[7] In this synthesis, we obtained the protected amino acid **8** as the precursor of (+)-**3**, possessing the Boc protected anino group and the benzyl ester, which is considered an useful substrate for the general amide-bond formation. After deprotection of the Boc group of **8** with TFA, the resulting amine TFA salt **17** (evaporated to dryness and used without purification) was coupled with (+)-**2** in the presence of a water-soluble carbodiimide to give **18** in 89% yield (Scheme 5). In a preliminary experiment, coupling between racemic **2** and **17** gave a mixture of the desired compound **18** and its diastereomer (inseparable on TLC), whose ^{1}H-NMR spectrum gave partially separated signals based on the respective diastereomers (ratio *ca.* 1:1). However, in the case of

coupling (+)-**2**, the ^{1}H-NMR spectrum of **18** was observed as the single diastereomer. This result means that the synthetic (+)-**2** has practical enantiomeric purity, and **18** can be regarded as optically pure. Deprotection of **18** by hydrogenolysis in the presence of 10% Pd-C in ethyl acetate provided (+)-**1** in 80% yield; mp 162-164℃; $[\alpha]_D^{22}$ +76.6°(*c* 2.20, MeOH) [lit. mp 161-163℃; $[\alpha]_D^{20}$ +68.4°(*c* 2.20, MeOH)].[1a,18] The spectral data of 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** has been accomplished. The yield was remarkably improved in contrast to the previous partial synthesis of (+)-**1** from natural **2**.



(a) TFA / CH_2Cl_2, 100% (b) EtN=C=N$(CH_2)_3NMe_2$·HCl, Et_3N, DMAP / CH_2Cl_2, 89%
(c) H_2, 10% Pd-C / EtOAc, 80%

Scheme 5

CONCLUSION

The asymmetric total synthesis of (+)-coronafacic acid (**2**) has been accomplished *via* our new approach, intramolecular 1, 6-conjugate addition, which provides the 1-hydrindanone framework of **2** possessing the desired functional groups and three stereogenic centers in a one-step reaction. The optically active ester (+)-**7**, which is the essential substrate for our synthesis on the optically active forms, has been efficiently synthesized by using catalytic asymmetric Michael addition. The effectiveness of our new approach is proved by the completion of the synthesis of (+)-**2** without any loss of the optical purity. The synthetic (+)-**2** has been converted into optically pure (+)-coronatine (**1**) *via* couping with the protected coronamic acid **17**, obtained from **8**, and subsequent deprotection. This first asymmetric total synthesis of (+)-**1** improved the yield of the previous partial synthesis and 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 study relating to jasmonic acid **4**. The study of structure-activity relationships by using the analogues of **1**, the biosynthetic precursors of **4**, and the amino acid conjugates of **4**, is also in progress.

EXPERIMENTAL SECTION

General Methods ^{1}H- and ^{13}C-NMR spectra were recorded with a JEOL JNM-EX-270 spectrometer (^{1}H: 270 MHz; ^{13}C: 67.8 MHz) or a Brucker AM-500 (^{1}H: 500 MHz; ^{13}C: 125 MHz) spectrometer, and chemical shifts are reported as δ (ppm) values relative to internal tetramethylsilane or the residual proton of deuterated solvent. IR spectra were measured with a Perkin Elmer System 2000 FT-IR spectrometer. Mass spectra were recorded with a JEOL JMS-AX500 spectrometer or a JEOL JMS-SX102A spectrometer. Specific

rotation values were measured with a JASCO DIP-370 digital polarimeter. Melting point values were obtained with a Yanaco micro-melting point apparatus MP-30 and are uncorrected. Column chromatography was carried out with Silica gel 60 (spherical, 70-140 mesh ASTM, KANTO CHEMICAL Co., Inc.).

Ethyl {1,4-dioxaspiro[4.4]non-7-yl}acetate [(±)-7]: To a stirred solution of **9** (4.56 g, 26.7 mmol) in benzene (100 ml) were added ethyleneglycol (3.0 mL, 54 mmol) and *p*-TsOH·H_2O (100 mg, 0.526 mmol). After being refluxed for 24 h under the conditions of azeotropic dehydration, the mixture was neutralized with $NaHCO_3$ (3.0 g), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane / EtOAc / Et_3N = 80 / 20 / 5) to give (±)-**7** (5.09 g, 89 %) as a colorless oil: IR (film) 2976, 2882, 1732, 1435, 1377, 1331, 1259, 1189, 1138, 1029, 1138, 1029, 947 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.19 (3H, t, *J* = 7.3 Hz, Me), 1.30 (1H, m, $C_{8'}$-H), 1.42 (1H, dd, *J* = 8.0, 13.3 Hz, $C_{6'}$-H), 1.66-1.94 (3H, m, $C_{8'}$-H, $C_{9'}$-H_2), 2.00 (1H, dd, *J* = 8.0, 13.3 Hz, $C_{6'}$-H), 2.30 (2H, d, *J* = 8.0 Hz, C_2-H_2), 2.35 (1H, sext., *J* = 8.0 Hz, $C_{7'}$-H), 3.76-3.90 (4H, m, OCH_2CH_2O), 4.06 (2H, q, *J* = 7.3 Hz, CH_2Me); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 14.20, 30.05, 33.98, 35.85, 40.24, 42.34, 60.15, 64.12, 64.21, 117.54, 172.68; EI-MS *m/z* (percent) 214 (2, M^+), 185 (55), 127 (84), 99 (100); HR-EI-MS calcd. for $C_{11}H_{18}O_4$ (M^+) *m/z* 214.1205, found 214.1169.

Ethyl (2*E*)-2-{1,4-dioxaspiro[4.4]non-7-yl}-4-ethyl-2,4-pentadienoate [(±)-11]: To a stirred solution of $(i\text{-Pr})_2NH$ (6.10 ml, 43.5 mmol) in dry THF (30 ml) was added 1.6 M hexane solution of *n*-BuLi (27.0 mL, 43.2 mmol) at 0 ℃ under Ar atmosphere. After being stirred for 30 min at 0 ℃, the solution was cooled to -78 ℃. To this LDA solution was added a solution of (±)-**7** (7.73 g, 36.1 mmol) in dry THF (10 ml), and the mixture was allowed to warm to -30 ℃ over 90 min. The resulting mixture was recooled to -78 ℃, and a solution of 2-ethylacrolein (5.0 mL, 51 mmol) in dry THF (10 ml) was added dropwise. After being kept with stirring for 2 h at -78 ℃, the reaction was quenched with sat. aq. NH_4Cl (100 ml), and the mixture was extracted with EtOAc (300 ml x 3). The combined extracts were washed with brine (50 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude products (±)-**10a** and (±)-**10b** (11.5 g) was directly used for the next reaction.

To a stirred solution of crude mixture (±)-**10a** and (±)-**10b** (11.5 g) in CH_2Cl_2 (30 ml), were added MsCl (5.6 mL, 72 mmol) and DMAP (17.6 g, 144 mmol). After being stirred for 48 h at r.t., the reaction mixrure was treated with 2N HCl (100 ml) and extracted with EtOAc (200 ml x 3). The combined extracts were washed with sat. aq. $NaHCO_3$ (200 ml) and brine (20 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude product (14.0 g) was directly used for the next reaction.

To a stirred solution of crude mesylate (14.0 g) in CH_2Cl_2 (30 ml) was added DBU (10 ml, 67 mmol), and the mixture was stirred for 24 h at r.t. After addition of 2N HCl (100 ml), the resulting mixture was extracted with EtOAc (200 ml x 3). The combined extracts were washed with sat. aq. $NaHCO_3$ (200 ml) and brine (20 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane / EtOAc = 8 / 2) to give (±)-**11** (7.70 g, 76 %, 3 steps) as a colorless oil: IR (film) 2969, 2880, 1713, 1623, 1456, 1367, 1324, 1251, 1118, 1027, 902, 773 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.03 (3H, t, *J* = 7.3 Hz, CH_2*Me*), 1.32 (3H, t, *J* = 7.3 Hz, CO_2CH_2*Me*), 1.73-1.83 (3H, m, $C_{6'}$-H, $C_{8'}$-H, $C_{9'}$-H), 1.95-2.08 (2H, m, $C_{8'}$-H, $C_{9'}$-H), 2.14 (2H, q, *J* = 7.3 Hz, CH_2Me),

2.27 (1H, t, J = 12.2 Hz, $C_{6'}$-H), 3.41 (1H, m, $C_{7'}$-H), 3.84-3.95 (4H, m, OCH_2CH_2O), 4.22 (2H, q, J = 7.3 Hz, CO_2CH_2Me), 4.88 (1H, br.s, C_5-H), 5.08 (1H, br.s, C_5-H), 7.03 (1H, s, C_3-H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 12.64, 14.25, 28.97, 29.40, 35.64, 36.03, 40.90, 60.38, 64.01, 64.55, 113.64, 117.93, 134.88, 141.47, 146.29, 167.40; EI-MS *m/z* (percent) 280 (10, M^+), 99 (100), 86 (88); HR-EI-MS calcd. for $C_{16}H_{24}O_4$ (M^+) *m/z* 280.1674, found 280.1680.

Ethyl (2*E*)-4-ethyl-2-(3-oxocyclopentyl)-2,4-pentadienoate [(±)-6]: To a stirred solution of (±)-**11** (500 mg, 1.78 mmol) in acetone (35 ml) was added *p*-TsOH·H_2O (10 mg, 53 μmol), and the mixture was stirred for 24 h at r.t. After addition of Et_3N (5.0 mL), the resulting mixture was concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane / EtOAc = 8 / 1) to give (±)-**6** (420 mg, 99 %) as a colorless oil: IR (film) 2969, 1747, 1714, 1624, 1463, 1405, 1368, 1338, 1253, 1156, 1097, 1026, 903, 775 cm^{-1}; ^{1}H-NMR (270 MHz, C_6D_6) δ 0.90 (3H, t, J = 7.3 Hz, CH_2Me), 1.01 (3H, t, J = 7.3 Hz, CO_2CH_2Me), 1.67-1.90 (2H, m, $C_{4'}$-H, $C_{5'}$-H), 1.95 (2H, q, J = 7.3 Hz, CH_2Me), 2.18 (1H, dd, J = 8.9, 18.1 Hz, $C_{2'}$-H), 2.23-2.35 (2H, m, $C_{4'}$-H, $C_{5'}$-H), 2.84 (1H, dd, J = 8.9, 18.1 Hz, $C_{2'}$-H), 3.52 (1H, quint., J = 8.9 Hz, $C_{1'}$-H), 4.02 (2H, q, J = 7.3 Hz, CO_2CH_2Me), 4.80 (1H, br.s, C_5-H), 4.97 (1H, br.s, C_5-H), 7.28 (1H, s, C_3-H); ^{13}C-NMR (67.8 MHz, C_6D_6) δ 12.69, 14.08, 28.40, 29.57, 35.73, 38.23, 43.01, 60.45, 113.77, 134.86, 141.80, 146.53, 166.44, 215.85; EI-MS *m/z* (percent) 236 (100, M^+), 149 (84); HR-EI-MS calcd. for $C_{14}H_{20}O_3$ (M^+) *m/z* 236.1412, found 236.1370.

Ethyl (3a*S, 6*R**, 7a*S**)-6-ethyl-2, 3, 3a, 6, 7, 7a-hexahydro-1-oxo-1*H*-indene-4-carboxylate [(±)-Coronafacic acid ethyl ester: (±)-5a] and Ethyl (3a*S**, 6*S**, 7a*S**)-6-ethyl 2, 3, 3a, 6, 7, 7a-hexahydro-1-oxo-1*H*-indene-4-carboxylate [(±)-C$_6$-*epi*-Coronafacic acid ethyl ester: (±)-5b]**: To a stirred solution of **6** (153 mg, 0.647 mmol) in EtOH (14 ml) was added NaH (80 mg, 2.0 mmol) at 0 ℃. The resulting mixture was allowed to warm to r.t. and stirred for 9 h. After successive addition of Et_2O (10 ml) and 2N HCl (5.0 ml), the reaction mixture was extracted with EtOAc (50 ml x 3). The combined extracts were washed with water (70 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane / EtOAc = 9 / 1) to give the mixture of (±)-**5a** and (±)-**5b** (3 : 1, 109 mg, 71 %) as a colorless oil. This mixture was separated by medium pressure column chromatography (hexane / ethyl acetate = 96 / 4).

(±)-**5a**: IR (film) 2964, 1747, 1715, 1645, 1464, 1382, 1255, 1146, 1098, 1069, 1034, 919, 818, 752 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.98 (3H, t, J = 7.3 Hz, CH_2Me), 1.09 (1H, dt, J = 10.9, 13.2 Hz, C_7-H), 1.32 (3H, t, J = 7.3Hz, CO_2CH_2Me), 1.43, 1.54 (each 1H, dquint., J = 7.3, 14.6 Hz, CH_2Me), 1.58 (1H, dt, J = 8.3,11.6 Hz, C_3-H), 1.86 (1H, dt, J = 13.2, 4.6 Hz, C_7-H), 2.20 (1H, ddt, J = 4.6, 13.2, 7.3 Hz, C_6-H), 2.27-2.46 (3H, m, C_2-H_2, C_{7a}-H), 2.56 (1H, dt , J = 11.6, 7.4 Hz, C_3-H), 3.08 (1H, dt, J = 11.6, 7.4 Hz, C_{3a}-H), 4.21 (2H, q, J = 7.3 Hz, CO_2CH_2Me), 6.92 (1H, s, C_5-H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 11.20, 14.29, 25.84, 27.84, 28.18, 36.25, 37.67, 38.15, 46.69, 60.47, 131.57, 143.85, 166.83, 220.48; EI-MS *m/z* (percent) 237 (13, M^++H), 236 (84, M^+), 119 (100); ER-EI-MS calcd. for $C_{14}H_{20}O_3$ (M^+) *m/z* 236.1412, found 236.1393.

(±)-**5b**: IR (film) 2964, 1743, 1715, 1644, 1464, 1366, 1253, 1144, 1085, 1063, 930, 890, 753 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 0.97 (3H, t, J = 7.3 Hz, CH_2Me), 1.32 (3H, t, J = 7.3 Hz, CO_2CH_2Me), 1.30-

1.45 (3H, m, C_7-H, CH_2Me), 1.90-2.02 (2H, m, C_3-*H*, C_7-*H*), 2.06 (1H, m, C_6-H), 2.15 (1H, dt, J = 8.4, 15.4 Hz, C_2-H), 2.20-2.29 (2H, m, C_2-*H*, C_3-*H*), 2.67 (1H, q, J = 6.0 Hz, C_{7a}-H), 3.26 (1H, q, J = 6.0 Hz, C_{3a}-H), 4.19-4.28 (2H, m, CO_2CH_2Me), 6.97 (1H, d, J = 2.3 Hz, C_5-H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 11.43, 14.27, 25.45, 26.96, 27.62, 34.63, 35.89, 36.77, 45.82, 60.47, 131.25, 144.89, 166.97, 221.24; EI-MS *m/z* (percent) 237 (16, M^++H) 236 (100, M^+), 119 (71); HR-EI-MS calcd. for $C_{14}H_{20}O_3$ (M^+) *m/z* 236.1412, found 236.1404.

Coronafacic acid [(±)-2]: A suspension of (±)-**5a** (168 mg, 0.711 mmol) in 3N HCl (40 mL) was refluxed for 4 h. After being cooled to r.t., the mixture was concentrated to one-half its initial volume under reduced pressure, extracted with with Et_2O (100 ml x 3). The combined extracts were washed with water (50 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography ($CHCl_3$ / EtOAc / AcOH = 60 / 40 / 1) to give (±)-**2** as a colorless oil, which was further recrystallized from acetone-H_2O (6 : 4) to give (±)-**2** (140 mg, 95 %) as colorless crystals: mp 125-128 ℃; IR (KBr) 2930, 1744, 1716, 1645, 1464, 1381, 1251, 1144, 1097, 888, 756 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.99 (3H, t, J = 7.4 Hz, CH_2*Me*), 1.09 (1H, dt, J = 11.2, 13.3 Hz, C_7-H), 1.44, 1.54 (each 1H, dquint., J = 14.8, 7.4 Hz, CH_2Me), 1.60 (1H, dq, J = 8.3, 12.2 Hz, C_3-H), 1.90 (1H, dt, J = 13.3, 4.8 Hz, C_7-H), 2.24 (1H, ddt, J = 4.8, 11.2, 7.4 Hz, C_6-H), 2.32 (1H, ddd, J = 6.1, 12.2, 18.4 Hz, C_2-H), 2.37 (1H, ddd, J = 4.8, 6.1, 13.3 Hz, C_{7a}-H), 2.41 (1H, dd, J = 8.3, 18.4 Hz, C_2-H), 2.61 (1H, dt ,J = 12.2, 6.1 Hz, C_3-H), 3.08 (1H, dt, J = 12.2, 6.1 Hz, C_{3a}-H), 7.08 (1H, s, C_5-H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 11.01, 25.61, 27.62, 28.02, 35.89, 37.77, 38.06, 46.51, 130.84, 146.77, 172.24, 220.41; EI-MS *m/z* (percent) 209 (14, M^++H), 208 (100, M^+), 119 (50); HR-EI-MS calcd. for $C_{12}H_{16}O_3$ (M^+) *m/z* 208.1099, found 208.1098; *Anal.* Cald. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74 %. Found: C, 69.09; H, 7.85 %.

Allyl *tert*-butyl malonate: To a stirred solution of *tert*-butyl methyl malonate (10.0 mL, 59.1 mmol) in methanol (150 ml) was added 1N NaOH (60 ml). After being stirred for 2 h at r.t., the reaction mixture was acidified with 2N HCl (40 ml) and then extracted with Et_2O (1000 ml x 3). The combined extracts were washed with water (500 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The resulting crude product was directly used for the next reaction.

To a stirred solution of the crude carboxylic acid in THF (200 ml) were added Et_3N (8.3 ml, 60 mmol) and allyl chloroformate (9.0 ml, 85 mmol). After being stirred for 2 h at 0 ℃, the reaction mixture was treated with 2N HCl (40 ml) and then extracted with Et_2O (500 ml x 3). The combined extracts were washed with sat. aq. $NaHCO_3$ (500 ml) and brine (20 ml), dried over anhydrous Na_2SO_4, concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane / EtOAc = 8 / 2) to give allyl *tert*-butyl malonate (6.88 g, 58 %, 2 steps) as a colorless oil: IR (film) 2982, 1732, 1650, 1370, 1332, 1279, 1144, 994, 935, 839, 760 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.47 (9H, s, CMe_3), 3.31 (2H, s, CH_2), 4.63 (2H, d, J = 5.6 Hz, $CH_2CH=CH_2$), 5.25 (1H, br.d, J = 11.2 Hz, CH=CH*H*), 5.35 (1H, br.d, J = 16.2 Hz, CH=CH*H*), 5.92 (1H, ddd, J = 5.6, 11.2, 16.2 Hz, $CH=CH_2$); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 27.91, 42.54, 65.86, 82.10, 118.63, 131.61, 165.62, 166.63; EI-MS *m/z* (percent) 200 (0.4, M^+), 127 (48), 57 (100); HR-EI-MS calcd. for $C_{10}H_{16}O_4$ (M^+) *m/z* 200.1048, found 200.1045.

Allyl *tert*-butyl [(1*R*)-4-oxocyclopent-2-enyl]malonate (13): To a stirred solution of **12** (2.38 g, 14.9 mmol) in toluene (70 ml) were added allyl *t*-butyl malonate (2.68 g, 13.4 mmol), K_2CO_3 (1.85 g, 13.4 mmol), and 18-Crown-6 (74 mg, 0.28 mmol) at 0 ℃. After being stirred for 48 h at 0 ℃, the reaction mixture was poured into water (50 ml), and extracted with CH_2Cl_2 (150 ml x 2). The combined extracts were dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane / EtOAc = 6 / 4) to give **13** (2.79 g, 74 %) as a colorless oil: $[\alpha]_D^{24}$ +73.2° (*c* 0.65, $CHCl_3$); IR (film) 2981, 1722, 1651, 1591, 1370, 1246, 1146, 992, 936, 842 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.44, 1.45 (each 4.5H, s, CMe_3), 2.26 (0.5H, dd, *J* = 2.0, 19.1 Hz, $C_{5'}$-H), 2.28 (0.5H, dd, *J* = 2.6, 19.1 Hz, $C_{5'}$-H), 2.62 (1H, dd, *J* = 6.6, 19.1 Hz, $C_{5'}$-H), 3.38 (0.5H, d, *J* = 7.9 Hz, C_2-H), 3.41 (0.5H, d, *J* = 7.3 Hz, C_2-H), 3.60 (1H, m, $C_{1'}$-H), 4.64 (2H, m, $CH_2CH=CH_2$), 5.26 (1H, br.d, *J* = 9.9 Hz, CH=CH*H*), 5.34 (1H, br.d, *J* = 17.5 Hz, CH=CH*H*), 5.88 (1H, m, C*H*=CH_2), 6.24 (1H, d, *J* = 6.6 Hz, $C_{3'}$-H), 7.68 (1H, m, $C_{2'}$-*H*); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 27.82 (4.5C), 27.85 (4.5C), 38.76 (0.5C), 38.85 (0.5C), 40.42 (0.5C), 40.47 (0.5C), 55.73 (0.5C), 55.83 (0.5C), 66.17, 83.04, 119.16, 131.25, 135.35, 164.28 (0.5C), 164.38 (0.5C), 166.43 (0.5C), 166.54 (0.5C), 167.56 (0.5C), 167.69 (0.5C), 207.91 (0.5C), 207.96 (0.5C); EI-MS *m/z* (percent) 280 (0.5, M^+), 224 (24), 207 (26), 180 (20), 139 (76), 57 (100); HR-EI-MS *m/z* calcd. for $C_{15}H_{20}O_5$ (M^+) 280.1311, found 280.1291.

[(1*S*)-4-Oxocyclopent-2-enyl]acetic acid (14): To a stirred solution of **13** (2.30 g, 8.21 mmol) in 1,4-dioxane (30 ml) were added $Pd(OAc)_2$ (37 mg, 0.16 mmol), PPh_3 (173 mg, 0.660 mmol), Et_3N (1.33 ml, 9.54 mmol), and formic acid (0.32 ml, 8.48 mmol). After being refluxed for 3 h, the reaction mixture was cooled to r.t., and concentrated under reduced pressure. The residue was dissolved in hexane-ether (1 : 1), and filtered through a plug of Celite. The filtrate was concentrated under reduced pressure to give the crude *t*-butyl [(1*S*)-4-oxocyclopent-2-enyl]acetate (2.0 g) as a pale yellow oil.

This crude *t*-butyl [(1*S*)-4-oxocyclopent-2-enyl]acetate (2.0 g) was dissolved in formic acid (20 ml) and the mixture was stirred for 2 h at. r.t. The reaction mixture was concentrated under reduced pressure. The resulting crude product was crystallized from ether-hexane (6 : 4) to give **14** as colorless crystals. The further recrystallization (twice from ether-hexane) gave **14** (518 mg, 45 %): mp 105-106 ℃; $[\alpha]_D^{23}$ +132° (*c* 1.00, $CHCl_3$); IR ($CHCl_3$) 3023, 1713, 1671, 1590, 1409, 1283, 1216, 1187, 880 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 2.11 (1H, dd, *J* = 1.3, 17.5 Hz, $C_{5'}$-H), 2.52 (1H, dd, *J* = 7.9, 16.8 Hz, C_2-H), 2.62 (1H, dd, *J* = 7.3, 16.8 Hz, C_2-H), 2.68 (1H, dd, *J* = 6.6, 17.5 Hz, $C_{5'}$-H), 3.38 (1H, ddddt, *J* = 1.3, 6.6, 7.3, 7.9, 2.3 Hz, $C_{1'}$-H), 6.24 (1H, dd, *J* = 2.3, 5.6 Hz, $C_{3'}$-H), 7.68 (1H, dd, *J* = 2.3, 5.6 Hz, $C_{2'}$-H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 37.31, 38.33, 40.63, 134.74, 166.34, 176.68, 209.11; EI-MS *m/z* (percent) 140 (100, M^+), 123 (6.6), 81 (62); HR-EI-MS *m/z* calcd. for $C_7H_8O_3$ (M^+) 140.0473, found 140.0472. *Anal.* Cald. for $C_7H_8O_3$: C, 60.00; H, 5.74 %. Found: C, 59.86; H, 5.74 %.

Ethyl {(7*S*)-1,4-dioxaspiro[4.4]non-7-yl}acetate [(+)-7]: To a stirred solution of **14** (514 mg, 3.67 mmol) in DMF (5.0 ml) were added $NaHCO_3$ (1.00 g, 9.98 mmol) and EtI (0.54 ml, 6.8 mmol). After being stirred for 6 h at r.t., the mixture was poured into water (100 ml), and extracted with EtOAc (200 ml x 3). The combined extracts were washed with brine (10 ml), and concentrated under reducced pressure. The residue was purified by silica gel column chromatography (hexane / AcOEt = 8 / 2) to give ethyl [(1*S*)-4-oxocyclopent-

2-enyl]acetate (566 mg, 91 %) as a colorless oil: $[\alpha]_D^{23}$ +116° (*c* 1.00, $CHCl_3$); IR (film) 1026, 1183, 1271, 1348, 1373, 1410, 1447, 1470, 1715, 1732, 2983 cm^{-1}; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.27 (3H, t, *J* = 7.3 Hz, Me), 2.07 (1H, dd, *J* = 2.0, 18.5 Hz, $C_{2'}$-H), 2.45 (1H, dd, *J* = 7.9, 15.8 Hz, C_2-H), 2.55 (1H, dd, *J* = 6.6, 15.8 Hz, C_2-H), 2.64 (1H, dd, *J* = 6.6, 18.5 Hz, $C_{5'}$-H), 3.38 (1H, dtq, *J* = 7.9, 6.6, 2.0 Hz, C_1-H), 4.16 (2H, q, *J* = 7.3 Hz, CH_2Me), 6.20 (1H, dd, *J* = 2.0, 5.3 Hz, $C_{3'}$-H), 7.65 (1H, dd, *J* = 2.0, 5.3 Hz, $C_{2'}$-H); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 14.20, 37.59, 38.78, 40.68, 60.83, 134.59, 166.36, 171.32, 208.75; EI-MS *m/z* (percent) 168 (64, M^+), 123 (42), 95 (100), 81 (24); HR-EI-MS *m/z* calcd. for $C_9H_{12}O_3$ (M^+) 168.0786, found 168.0773.

To a solution of ethyl [(1*S*)-4-oxocyclopent-2-enyl]acetate (463 mg, 2.76 mmol) in EtOH (4.0 ml) was added 10 % Pd-C (30 mg). The mixture was vigorously stirred for 24 h at r.t. under hydrogen atmosphere. The mixture was filtrated and the catalyst was washed with EtOAc (20 ml). The combined filtrate and washings were concentrated under reduced pressure to give a crude ethyl [(1*S*)-3-oxocyclopentyl]acetate as a colorless oil.

To a stirred solution of crude ethyl [(1*S*)-3-oxocyclopentyl]acetate in benzene (30ml) were added PPTS (20 mg, 0.08 mmol), and ethyleneglycol (0.33 ml, 5.9 mmol). After being refluxed for 24 h under the conditions of azeotropic dehydration, the mixture was neutralized with $NaHCO_3$ (1.0 g), and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane / AcOEt / Et_3N = 80 / 20 / 5) to give (+)-**7** (502 mg, 85 %, 2 steps, 96 % e.e.) as a colorless oil: $[\alpha]_D^{23}$ +3.6° (*c* 1.00, $CHCl_3$); EI-MS *m/z* (percent) 214 (2, M^+), 185 (55), 127 (84), 99 (100); HR-EI-MS calcd. for $C_{11}H_{18}O_4$ (M^+) *m/z* 214.1205, found 214.1171. The other spectral data (IR, ^{1}H- and ^{13}C-NMR) were completely identical with those of (±)-**7**.

Preparation of 0.05 M Ga-Na-(*S*)-BINOL in THF-Et_2O solution:[14c] To a solution of NaO-*t*-Bu (2.88 g, 30.0 mmol) in THF (52 ml) was added (*S*)-BINOL (4.29 g, 15.0 mmol) in THF (45 ml) at r.t. After being stired for 0.5 h, the resulting THF solution of (*S*)-BINOL disodium salt was added to $GaCl_3$ (1.32 g, 7.5 mmol) in THF-Et_2O (5 : 2) solution (53 ml), and the mixture was stirred for 3 h at r.t. The solution was kept standing for one day to precipitate NaCl salt, and the supernatant was used as 0.05 M Ga-Na-(*S*)-BINOL in THF-Et_2O (9 : 1) solution.

Diethyl [(1*S*)-3-oxocyclopentyl]malonate (15): To a stirred solution of 0.05 M Ga-Na-(*S*)-BINOL in THF-Et_2O (9 : 1) (40 ml, 10 mol %) was added NaO-*t*-Bu (134 mg, 1.39 mmol, 7.0 mol %) in THF (4.0 ml) at r.t. To present solution was added 2-cyclopentenone (1.67 ml, 19.9 mmol) and diethyl malonate (3.04 ml, 20.0 mmol) at r.t. After being stirred for 30 h at r.t., the reaction mixture was treated with 1N HCl (50 ml) and then extracted with EtOAc (200 mL x 3). The combined extracts were washed with brine (50 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was perified by silica gel column chromatography (hexane / acetone = 8 / 2) to give **15** (4.60 g, 95 %) as a colorless oil: $[\alpha]_D^{24}$ -82.7 (*c* 1.00); IR (film) 2983. 2908, 1732, 1465, 1370, 1096, 1031, 859; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.25, 1.27 (each 3H, t, *J* = 7.3 Hz, Me x 2), 1.66 (1H, m, $C_{5'}$-H), 2.00 (1H, dd, *J* = 10.9, 18.4 Hz, $C_{2'}$-H), 2.11~2.38 (3H, m, $C_{4'}$-H_2, $C_{5'}$-H), 2.49 (1H, dd, *J* = 7.3, 18.4 Hz, $C_{2'}$-H), 2.86 (1H, m, C_1-H), 3.32 (1H, d, *J* = 9.2 Hz, C_2-H), 4.18, 4.21 (each 2H, q, *J* = 7.3 Hz, CH_2Me); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 14.02, 27.44, 36.28, 38.15, 42.86, 56.48, 61.55, 168.01, 168.10, 217.09; EI-MS *m/z* (percent) 243 (0.6, M^++H), 197 (34,

M^+-OEt), 160 (100); HR-EI-MS calcd. for $C_{12}H_{19}O_5$ (M^++H), *m/z* 243.1233, found 243.1210.

Diethyl {(7*S*)-1,4-dioxaspiro[4.4]non-7-yl}malonate (16): To a stirred suspension of **15** (4.36 g, 18.0 mmol) in ethyleneglycol (18.0 ml) and 2-ethyl-2-methyl-1,3-dioxolane (30 ml) was added *p*-TsOH·H_2O (75 mg, 0.39 mmol). After being stirred for 24 h at 50 ℃, the mixture was poured into 30 % aq. $NaHCO_3$ (100 mL), and extracted with EtOAc (200 ml x 3). The combined extracts were washed with water (200 ml) and brine (50 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane / acetone / Et_3N = 80 / 20 / 1) to give **16** (4.27 g, 88 %) as a colorless oil: $[\alpha]_D^{21}$ +4.0 (*c* 1.00); IR (film) 2982, 2883, 1733, 1465, 1370, 1150, 1029, 948; ^{1}H-NMR (270 MHz, $CDCl_3$) δ 1.26 (6H, t, *J* = 7.3 Hz, Me x 2), 1.48 (1H, m, $C_{8'}$-H), 1.60 (1H, dd, *J* = 8.2, 13.5 Hz, $C_{6'}$-H), 1.78-2.05 (3H, m, $C_{8'}$-H, $C_{9'}$-H_2), 2.13 (1H, dd, *J* = 7.9, 13.5 Hz, $C_{6'}$-H), 2.72 (1H, m, $C_{7'}$-H), 3.30 (1H, d, *J* = 9.9 Hz, C_2-H), 3.89-3.97 (4H, m, OCH_2CH_2O), 4.21, 4.22 (each 2H, q, *J* = 7.3 Hz, CH_2Me); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 14.09, 28.25, 35.55, 36.73, 40.63, 57.16, 61.28, 64.26, 117.05, 168.57, 168.64; EI-MS *m/z* (percent) 286 (1.9, M^+), 241 (34, M^+-OEt), 127 (100); HR-EI-MS calcd. for $C_{14}H_{22}O_6$ (M^+), *m/z* 286.1416, found 286.1399.

Ethyl {(7*S*)-1,4-dioxaspiro[4.4]non-7-yl}acetate [(+)-7]: To a stirred solution of **16** (4.21 g, 15.7 mmol) in DMSO (70 ml) and H_2O (0.36 ml, 20 mmol) was added LiCl (1.30 g, 30.7 mmol). After being stirred for 4 h at 180 ℃, the mixture was cooled to r.t., poured into sat. aq. NH_4Cl (100 mL), and extracted with EtOAc (200 ml x 3). The combined extracts were washed with water (100 ml) and brine (30 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane / acetone / Et_3N = 85 / 15 / 1) to give (+)-**7** (2.81 g, 84 %, 98 % e.e.) as a colorless oil: $[\alpha]_D^{21}$ +4.1° (*c* 1.00, $CHCl_3$); EI-MS *m/z* (percent) 214 (2.7, M^+), 185 (69), 127 (87), 99 (100); HR-EI-MS calcd. for $C_{11}H_{18}O_4$ (M^+) *m/z* 214.1205, found 214.1175. The other spectral data (IR, ^{1}H- and ^{13}C-NMR) were completely identical with those of (±)-**7**.

Ethyl (2*E*)-2-{(7*S*)-1,4-dioxaspiro[4.4]non-7-yl}-4-ethyl-2,4-pentadienoate [(-)-11]: By the three-steps conversion as described in the synthesis of (±)-**11**, (-)-**11** (3.30 g, 90 %) was obtained from (+)-**7** (2.80 g, 98 % e.e.): $[\alpha]_D^{22}$ -11.2° (*c* 1.00, $CHCl_3$); EI-MS *m/z* (percent) 280 (34, M^+), 235 (39), 99 (100); HR-EI-MS calcd. for $C_{16}H_{24}O_4$ (M^+) *m/z* 280.1674, found 280.1664. The other spectral data (IR, ^{1}H- and ^{13}C-NMR) were completely identical with those of (±)-**11**.

Ethyl (2*E*)-4-ethyl-2-[(7*S*)-3-oxocyclopentyl]-2,4-pentadienoate [(-)-6]: By the same method as described in the synthesis of (±)-**6**, (-)-**6** (2.60 g, 94 %) was obtaine from (-)-**11** (3.30 g): $[\alpha]_D^{22}$ -39.4° (*c* 1.00, $CHCl_3$); EI-MS *m/z* (percent) 236 (24, M^+), 91 (100); HR-EI-MS calcd. for $C_{14}H_{20}O_3$ (M^+) *m/z* 236.1412, found 236.1444. The other spectral data (IR, ^{1}H- and ^{13}C-NMR) were completely identical with those of (±)-**6**.

Ethyl (3a*S*, 6*R*, 7a*S*)-6-ethyl-2,3,3a,6,7,7a-hexahydro-1-oxo-1*H*-indene-4-carboxylate [(+)-Coronafacic acid ethyl ester] [(+)-5a] and Ethyl (3a*S*, 6*S*, 7a*S*)-6-ethyl 2,3,3a,6,7,7a-hexahydro-1-oxo-1*H*-indene-4-carboxylate [(+)-C_6-*epi*-Coronafacic acid ethyl ester] [(+)-

5b]: By the same method as descrived in the synthesis of (±)-**5a** and (±)-**5b**, (+)-**5a** and (+)-**5b** (354 mg, 76 %, 3 : 1) was obtaine from (-)-**6** (473 mg).

(+)-**5a**: $[\alpha]_D^{22}$ +89.8° (*c* 1.00, $CHCl_3$); EI-MS *m/z* (percent) 237 (13, M^++H), 236 (18, M^+), 119 (64), 91 (100); ER-EI-MS calcd. for $C_{14}H_{20}O_3$ (M^+) *m/z* 236.1412, found 236.1390. The other spectral data (IR, ^{1}H- and ^{13}C-NMR) were completely identical with those of (±)-**5a**.

(+)-**5b**: $[\alpha]_D^{24}$ +142° (*c* 1.13, $CHCl_3$); EI-MS *m/z* (percent) 237 (16, M^++H) 236 (93, M^+), 119 (100); HR-EI-MS calcd. for $C_{14}H_{20}O_3$ (M^+) *m/z* 236.1412, found 236.1404. The other spectral data (IR, ^{1}H- and ^{13}C-NMR) were completely identical with those of (±)-**5b**.

Coronafacic acid [(+)-2]: By the same method as described in the synthesis of (±)-**2**, (+)-**2** (287 mg, 50 %, after recrystallization) was obtained from (+)-**5a** (653 mg).[16] In this case (the largest scale-reaction among our trials), the tarry matter was co-produced. In smaller scale-reactions, the yields were approximately 70% after recrystallization: mp142-143℃; $[\alpha]_D^{22}$ +122° (*c* 1.00, MeOH); IR (KBr) 3223, 1717, 1637, 1381, 1224, 1198, 1105, 825, 694 cm^{-1}; EI-MS *m/z* (percent) 209 (13, M^++H), 208 (100, M^+), 119 (45); HR-EI-MS calcd. for $C_{12}H_{16}O_3$ (M^+) *m/z* 208.1099, found 208.1098. *Anal.* Cald. for $C_{12}H_{16}O_3$: C, 69.21; H, 7.74 %. Found: C, 69.11; H, 7.77 %. The other spectral data (IR, ^{1}H- and ^{13}C-NMR) were completely identical with those of (±)-**2**.

Coronatine benzyl ester (18): To a stirred solution of **8** (130 mg, 0.407 mmol) in CH_2Cl_2 (1.5 ml) was added TFA (1.5 ml). After being stirred for 2 h at r.t., the mixture was concentrated under reduced pressure. The residual TFA was removed by co-evaporation with benzene. The resulting amine TFA salt (**17**) was directly used for the next reaction.

To a solution of (+)-**2** (78 mg, 0.37 mmol) in CH_2Cl_2 (1.5 ml) were added Et_3N (0.36 ml, 2.6 mmol), DMAP (70 mg, 0.57 mmol), and WSC (230 mg, 1.20 mmol) at 4 ℃, and the mixture was stirred for 10 min at 4 ℃. To the present mixture containning the activated carboxylic acid was added a solution of previously prepared **17** in CH_2Cl_2 (2.0 ml). After being stirred for 24 h at r.t., the reaction mixture was treated with 2N HCl and the extracted with EtOAc (30 ml x 3). The combined extracts were washed with sat. aq. $NaHCO_3$ (10 ml) and brine (10 ml), dried over anhydrous Na_2SO_4, and concentrated under reduced pressure. The residue was purified by silica gel column chromatography (hexane / EtOAc = 6 / 4) to give **18** (134 mg, 89 %) as a colorless oil: $[\alpha]_D^{22}$ +52.0° (*c* 1.00, $CHCl_3$); IR (film) 2963, 1732, 1661, 1627, 1516, 1506, 1456, 1380, 1329, 1161, 751, 698 cm^{-1}; ^{1}H-NMR (270 MHz, C_6D_6) δ 0.75 (3H, t, *J* = 7.3 Hz, CH_2*Me*), 0.81 (1H, m, C_7-H), 0.98 (3H, t, *J* = 7.3 Hz, C_5-H_2*Me*), 1.02-1.33 (6H, m, C_3-H, C*H*$_2$Me, coronamic acid's CH and CH_3), 1.61-1.77 (4H, m, C_6-H, C_7-H, coronamic acid's C*H*$_2$Me), 1.85 (1H, ddd, *J* = 6.6, 11.5, 18.5 Hz, C_2-H), 2.00-2.09 (2H, m, C_2-H, C_{7a}-H), 2.15 (1H, dt, *J* = 11.6, 6.6 Hz, C_3-H), 2.95 (1H, dt, *J* = 11.5, 6.6 Hz, C_{3a}-H), 5.04, 5.12 (each 1H, d, *J* = 12.2 Hz, C*H*$_2$Ph), 5.76 (1H, s, NH), 5.98 (1H, s, C_5-H), 7.00-7.24 (5H, m, Ph-H); ^{13}C-NMR (67.8 MHz, C_6D_6) δ 11.34, 13.66, 20.80, 23.47, 26.26, 27.88, 28.27, 33.14, 36.38, 37.24, 37.90, 38.55, 46.17, 67.07, 128.58, 128.63, 135.66, 136.46, 136.82, 138.83, 168.83, 170.95, 217.72; FD-MS *m/z* (percent) 409 (M^+), HR-FD-MS calcd. for $C_{25}H_{31}NO_4$ (M^+)*m/z* 409.2250, found 409.2244.

Coronatine [(+)-1]: To a solution of **18** (149 mg, 0.364 mmol) in EtOAc (8.0 ml) was added 10 % Pd-C (75 mg). The mixture was vigorously stirred for 20 min at r.t. under hydrogen atmosphere. The reaction mixture was filtrated and the catalyst was washed with EtOAc (5 ml x 3). The combined filtrate and washings were concentrated under reduced pressure to give a crude product (116 mg, quant.). Purification by silica gel column chromatography (CH_3Cl / MeOH = 5 / 1) gave (+)-**1** as a colorless amorphous powder, which was further recrystallized from EtOAc-hexane to give (+)-**1** (93 mg, 80 %) as white crystals: mp 162-164℃; $[\alpha]_D^{22}$ +76.6° (*c* 2.20, MeOH); IR (KBr) 3270, 2924, 1735, 1655, 1624, 1523, 1459, 1263, 1173, 1048 cm^{-1}; ^{1}H-NMR (500 MHz, $CDCl_3$) δ 0.97 (3H, t, *J* = 7.4 Hz, CH_2*Me*), 1.02 (3H, t, *J* = 7.3 Hz, coronamic acid's CH_2*Me*), 1.03 (1H, q, *J* = 11.1 Hz, C_7-H), 1.22-1.30 (2H, m, coronamic acid's CH_2), 1.39 (1H, dq, *J* = 15.0, 7.4 Hz, C*H*HMe), 1.43-1.70 (5H, m, C_3-H, C*H*HMe, coronamic acid's C*H*$_2$Me and CH), 1.88 (1H, dt, *J* = 4.8, 11.1 Hz, C_7-H), 2.20-2.24 (1H, m, C_6-H), 2.25-2.42 (3H, m, C_2-H_2, C_{7a}-H), 2.46 (1H, dt, *J* = 12.1, 6.1 Hz, C_3-H), 3.15 (1H, dt, *J* = 12.1, 6.1 Hz, C_{3a}-H), 6.33 (1H, s, C_5-H), 6.50 (1H, s, NH); ^{13}C-NMR (67.8 MHz, $CDCl_3$) δ 11.29, 13.43, 20.54, 22.82, 25.90, 27.75, 28.03, 33.77, 36.10, 37.25, 38.12, 46.33, 93.17, 135.31, 137.47, 169.99, 220.47 (The only one ^{13}C-signal of amide or carboxylic acid could not be observed even increasing the accumulation and changing parameters.); EI-MS *m/z* (percent) 319 (M^+, 41), 301 (10), 191 (100), 163 (26), 119 (21); HR-EI-MS calcd. for $C_{18}H_{25}O_4N$ (M^+) *m/z* 319.1783, found 319.1782: *Anal.* Calcd. for $C_{18}H_{25}O_4N$: C, 67.69; H, 7.89; N, 4.39 %. Found: C, 67.25; H, 7.85; N, 4.35 %.

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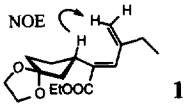
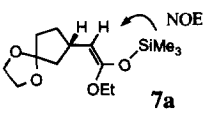
9. The NOE-enhancement as shown below was observed. This result is explicable that **11** possesses (*E*)-geometry and *s-cis* conformation.

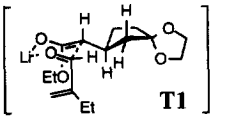


11

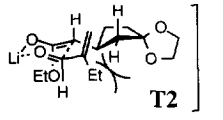
10. The (*E*)-geometry of lithium enolate of **7** was determined as the corresponding silyl enol ether **7a** (LDA/ THF, then TMSCl). The NOE-enhancement of the olefinic proton was observed by the irradiation of the methyl protons in the TMS group. In two possible 6-membered chair-like transition states (**T1** and **T2**), **T1** predominates over **T2** because the steric hindrance between the bulky cyclopentane moiety of the enolate and the alkenyl moiety of the aldehyde contributes unfavorably in **T2**. In **T1**, the interaction between the cyclopentane moiety and the hydrogen is not significant in contrast to **T2**. Therefore, aldol condensation proceeds exclusively *via* **T1** to give *syn*-products (**10a** and **10b**).



7a



T1



T2

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13. Column: CHIRALCEL OC® (ϕ4.6 x 250 mm), Eluent: hexane/2-propanol (96/4), Flow rate: 0.3 ml/min, Detection: UV 220 nm, Retention time: (+)-**7**/ 36 min; (-)-**7**/ 40 min
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15. Column: CHIRALCEL OC® (ϕ4.6 x 250 mm), Eluent: hexane/2-propanol (96/4), Flow rate: 0.3 ml/min, Detection: UV 240 nm, Retention time: (+)-**5a**/ 64 min; (-)-**5a**/ 59 min
16. The acidic hydrolysis of **5a** is heterogeneous reaction and requires vigourous stirring under refluxing conditions. Therefore, the effectiveness of stirring influences the reaction period and yields. The smaller scale-reactions (well-stirred conditions) provide high yields within shorter time in our experience. In contrast to this, the larger scale-reactions provide moderate yields caused by the appearence of decomposed tarry matter, depending on elongation of reaction time. The conditions using co-solvent have been examining.
17. Although the first reported mp of natural (+)-**2** is described as 125-126°C in ref. 1a, the corrected mp is described as 141-142°C in the thesis of Dr. K. Shiraishi, Chemical Structure and Biological Activity of Coronatine, Hokkaido University, 1978. Furthermore, Prof. M. Nakayama reports mp 142-143°C for his synthetic (+)-**2** ($[\alpha]_D^{20}$ +109°) and our natural sample in ref. 3g.
18. Although the mp of natural coronatine 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 present time, the specific rotations, which may be influenced by the temperature, can not be compared directly. Coronatine obtained by the partial synthesis[1b] showed $[\alpha]_D^{20}$ +78.8° (*c* 1.20, MeOH).

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