Received: 28 November 2019 | Revised: 15 December 2019 | Accepted: 18 December 2019

DOI: 10.1002/chir.23172

WILEY

SPECIAL ISSUE ARTICLE

A scalable synthesis of (+)-coronafacic acid

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Funding information
Japan Society for the Promotion of Science, Grant/Award Numbers: A3 Foresight Program, Core-to-Core Program Asian Chemical Biology Initia; Ministry of Education, Culture, Sports, Science and Technology, Grant/Award Numbers: 17H00885, 17H06407, 19K06968, 26282207; SUNBOR GRANT

Abstract

A facile, efficient, and scalable synthesis of optically pure coronafacic acid by resolution of racemic coronafacic acid obtained using an improved version of Watson's method has been developed. By optimizing the boron-mediated aldol reaction of Watson, we were able to prepare 2.1 g of racemic coronafacic acid. This was coupled with (S)-4-isopropyl-2-oxazolidinone to give a mixture of diastereomeric coronafacyl oxazolidinones, which were readily separable by silica-gel column chromatography to give 630 mg of optically pure (+)-coronafacic acid.

KEYWORDS

boron-mediated aldol reaction, coronafacic acid, coronatine, jasmonates, optical resolution

1 | INTRODUCTION

(+)-Coronatine (**1**) is a natural phytotoxin produced by *Pseudomonas syringae*[1] and a functional mimic of the active form of the plant hormone (+)-7-*iso*-jasmonoyl-L-isoleucine (2).[2] In plants, **1** and **2** target the COI1-JAZ co-receptor[3] to induce a defense response against attack by necrotrophic pathogens and herbivorous insects (Figure 1).[4] Both **1** and **2** are in principle important chemical tools in the field of jasmonate biology, but as **2** is prone to epimerize under physiological conditions at the 7 position to afford a biologically inactive epimer,2b **1** has seen more widespread use and has enabled the development of further useful chemical tools.[5]

Structurally, **1** consists of a (+)-coronafacic acid (**3**) bonded to (+)-coronamic acid (**4**), an unusual α-amino acid. Past syntheses of 1 have been accomplished on a small scale by synthesizing **3** and condensing it with **4** (which can be easily prepared at scale),[6] but no published route to **3** is of any practical use,[6] being unable to supply sufficient optically pure **3** for subsequent experimentation. Recently, however, Watson reported a synthesis of **(±)-3** in only 10 steps and 10% overall yield on a scale of 2.7 g.[7] However, there were some drawbacks with this method: the boron aldol step was low-yielding and capricious, and no procedure to obtain optically pure **3** from the racemic product of the reaction was disclosed. In this study, we improved the Watson method, perfected a method for the resolution of the racemic product, and finally obtained scalable quantities of optically pure **(+)-3** in 15% overall yield.

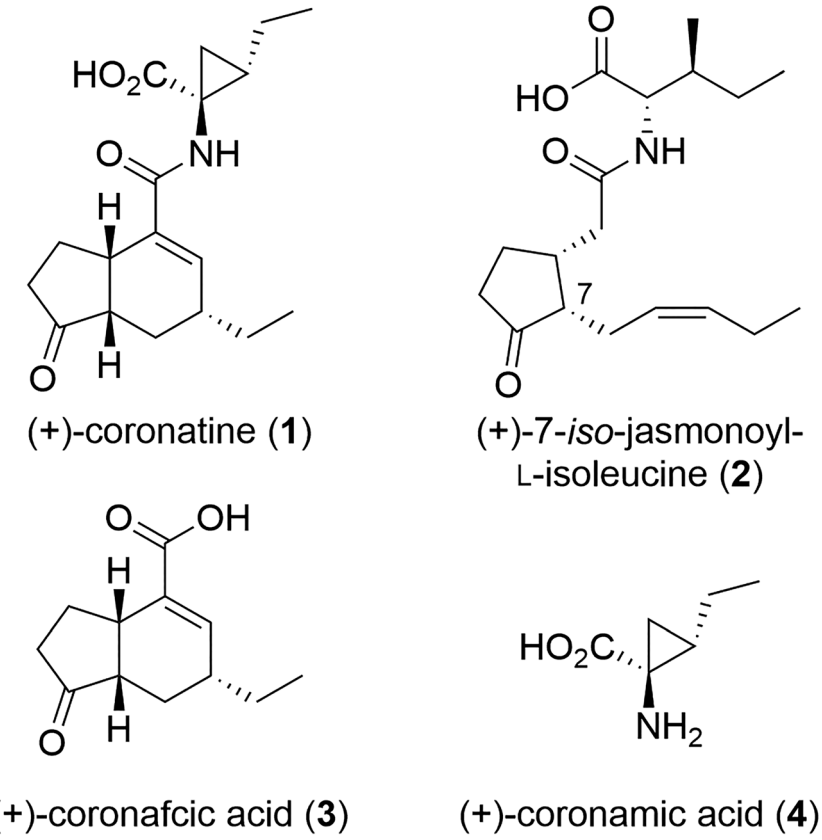


FIGURE 1 (+)-Coronatine (**1**), (+)-7-*iso*-jasmonoyl-L-isoleucine (**2**), (+)-coronafacic acid (**3**), and (+)-coronamic acid (**4**)

2 | MATERIALS AND METHODS

2.1 | General

All chemical reagents and solvents were obtained from commercial suppliers (Kanto Chemical Co, Ltd; Wako Pure Chemical Industries Co, Ltd; Nacalai Tesque Co, Ltd; Tokyo Chemical Industry Co, Ltd; Sigma-Aldrich Co, LLC; and GE Healthcare) and used without further purification. Reversed-phase high–performance liquid chromatography (HPLC) was carried out on a PU-4180 plus pump equipped with UV-4075 and MD-4010 detectors (JASCO, Tokyo, Japan). Both ^{1}H and ^{13}C NMR spectra were recorded on a JNM-ECS-400 spectrometer (JEOL, Tokyo, Japan) in deuterated chloroform and using TMS as an internal standard. Fourier transform infrared (FT/IR) spectra were recorded on an FT/IR-4100 (JASCO, Tokyo, Japan). High-resolution (HR) electrospray ionization (ESI)–mass spectrometry (MS) analyses were conducted using a microTOF II (Bruker Daltonics Inc, Billerica, MA). Optical rotation was measured by a JASCO P-2200 polarimeter (JASCO, Tokyo, Japan). All anhydrous solvents were either dried by standard techniques and freshly distilled before use or purchased in anhydrous form. Flash chromatography was performed on Isolera system (Biotage Ltd, North Carolina, US). TLC was performed on Silica gel F254 (0.25 or 0.5 mm, MERCK, Germany) or RP-18F254S (0.25 mm, MERCK). All reactions were carried out under air unless stated otherwise.

2.2 | Synthesis of (+)-coronafacic acid

2.2.1 | Boron-mediated aldol reaction

Dibutylboryl trifluoromethanesulfonate solution (1M in CH_2Cl_2) (30.4 mL, 30.4 mmol) was added to a solution of ester **9** (5.0 mL, 30.4 mmol) in anhydrous CH_2Cl_2 (200 mL) and DIPEA (8.1 mL, 46.7 mmol) in a three-necked flask at room temperature under an atmosphere of argon, and the resulting solution stirred at room temperature for 3 minutes. A solution of aldehyde **8** (3.65 g, 23.3 mmol) in CH_2Cl_2 (40 mL) was added and the reaction mixture was stirred at room temperature for 1 hour. The reaction was quenched by sequential addition of potassium buffer solution (pH 7.4, 50 mL), MeOH (80 mL), and H_2O_2 (30% solution, 25 mL). The reaction mixture was stirred vigorously at room temperature for 14 hours, diluted with water (50 mL), and extracted with CH_2Cl_2. The solution was extracted four times with CH_2Cl_2, and the combined organic layers were washed with brine. The organic layer was dried over anhydrous Na_2SO_4 and concentrated under reduced pressure.

The crude product was purified by medium-pressure chromatography (Isolera, eluent: 5:95 *n*-hexane/EtOAc hexane to 40:60 *n*-hexane/EtOAc) to afford 10 (7.26 g, 81%, *syn*:*anti* = 90:10) as yellow oil.

2.2.2 | Synthesis of 13 and 14

PivCl (2.1 mL, 13.7 mmol) was added to a solution of (±)-coronafacic acid ((±)-**3**) (1.90 g, 9.10 mmol) and Et_3N (7.9 mL, 48.5 mmol) in CH_2Cl_2 (100 mL), and the mixture was stirred for 2 hours. The resulting solution was added to a mixture of LiCl (1.70 g, 27.5 mmol), (*S*)-4-isopropyl-2-oxazolidinone (2.42 g, 18.2 mmol), and DMAP (110 mg, 910 μmol) at room temperature, and the mixture was stirred for 16 hours. The reaction was quenched with 1M HCl, and the mixture was extracted with CH_2Cl_2. The combined organic layers were washed with brine, dried over Na_2SO_4, and concentrated under reduced pressure. The crude product was purified by silica-gel column chromatography (AcOEt/*n*-hexane = 80/20) to afford **13** and **14**.

Compound **13**: yellow oil, 1.20 g, 41% yield. $[\alpha]^{22}_D$ = +87.0 (c = 1.81, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$); δ_H 6.27 (s, 1H), 4.59 (ddd, *J* = 8.9, 6.1, 4.6 Hz, 1H), 4.33 (t, *J* = 8.9Hz, 1H), 4.17 (dd, *J* = 8.9, 6.1 Hz, 1H), 3.31 (dt, *J* = 9.7, 7.4 Hz, 1H), 2.48-2.13 (m, 6H), 1.88 (dt, *J* = 13.0, 4.7 Hz, 1H), 1.76 (ddd, *J* = 10.0, 7.9, 7.0 Hz, 1H), 1.54-1.46 (m, 2H), 1.27 (dt, *J* = 13.0, 10.0 Hz, 1H), 0.97 (t, *J* = 7.4 Hz, 3H), 0.94 (d, *J* = 6.9 Hz, 3H), 0.93 (d, *J* = 6.9 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); δ_C 219.99, 170.38, 153.73, 141.32, 133.75, 63.27, 57.84, 46.07, 37.87, 37.19, 36.02, 28.31, 27.57, 26.66, 25.65, 17.80, 15.16, 11.22; IR (film) cm^{-1}: 2962, 1782, 1739, 1682, 1288, 756; HRMS (ESI, positive) *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{25}NO_4Na$: 342.1676, found: 342.1669.

Compound **14**: yellow oil, 1.18 g, 40% yield. $[\alpha]^{22}_D$ = +21.4 (c = 1.79, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$); δ_H 6.08 (s, 1H), 4.44 (dt, *J* = 8.7, 4.0 Hz, 1H), 4.31 (t, *J* = 8.7 Hz, 1H), 4.17 (dd, *J* = 8.7, 4.0 Hz, 1H), 3.08 (dt, *J* = 10.0, 7.5 Hz, 1H), 2.58-2.16 (m, 6H), 1.91-1.82 (m, 2H), 1.56-1.35 (m, 2H), 1.21 (dt, *J* = 13.0, 10.5 Hz, 1H), 0.95 (t, *J* = 7.4 Hz, 3H), 0.95 (d, *J* = 7.0 Hz, 3H), 0.91 (d, *J* = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$); δ_C 219.89, 170.44, 153.53, 138.79, 133.11, 63.26, 59.03, 46.26, 38.00, 36.97, 36.93, 28.29, 27.71, 27.53, 25.66, 17.95, 14.75, 11.15; IR (film) cm^{-1}: 2962, 1786, 1739, 1689, 1300, 748; HRMS (ESI, positive) *m*/*z* $[M + Na]^+$ calcd for $C_{18}H_{25}NO_4Na$: 342.1676, found: 342.1679.

2.2.3 | Synthesis of (+)-coronafacic acid ((+)-3)

30% H_2O_2 aq. (1.5 mL, 14.7 mmol) was added dropwise at 0°C to a solution of compound **13** (1.10 g, 5.29 mmol) and lithium hydroxide monohydrate (290 mg, 6.91 mmol) in a mixture of THF (60 mL) and water (20 mL). The mixture was stirred at room temperature for 2.5 hours. The reaction mixture was acidified to pH 2 with 1M HCl. The solution was extracted three times with AcOEt, and the combined organic layers were washed with brine. The organic layer was dried over anhydrous Na_2SO_4. The crude product was purified by silica-gel column chromatography ($E_{t2}O$/*n*-hexane/AcOH = 70/30/0.5) to afford **(+)-3** (631 mg, 89%) as a white solid. $[\alpha]^{25}_D$ = +121 (c 0.98, MeOH). All spectral data of (+)-**3** were identical to those reported.[8]

2.2.4 | Synthesis of (−)-coronafacic acid ((−)-3)

30% H_2O_2 aq. (1.5 mL, 14.7 mmol) was added dropwise at 0°C to a solution of compound **14** (1.10 g, 5.29 mmol) and lithium hydroxide monohydrate (290 mg, 6.91 mmol) in a mixture of THF (60 mL) and water (20 mL). The mixture was stirred at room temperature for 3.5 hours. The reaction mixture was acidified to pH 2 with 1M HCl. The solution was extracted three times with AcOEt, and the combined organic layers were washed with brine. The organic layer was dried over anhydrous Na_2SO_4. The crude product was purified by silica-gel column chromatography ($E_{t2}O$/*n*-hexane/AcOH = 70/30/0.5) to afford (−)-**3** (579 mg, 81%) as a white solid. $[\alpha]^{25}_D$ = −118 (c 1.01, MeOH). All spectral data of (−)-**3** were identical to those previously reported.[9]

2.3 | Chiral HPLC analysis

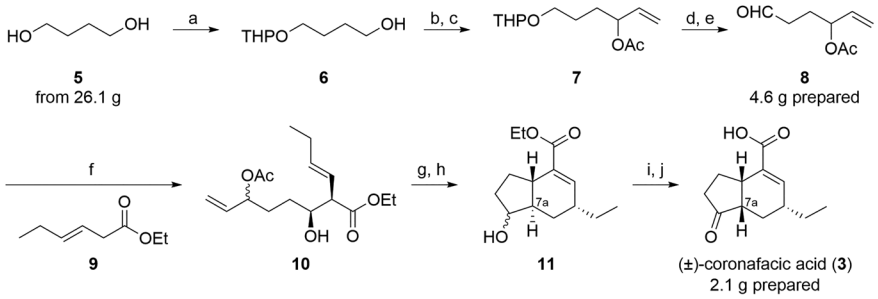
2.3.1 | Coronafacic acid methyl ester 17 and *ent*-17

Optical purities were determined by chiral HPLC analyses on a Chiralpak IA ϕ4.6 × 250 mm column (Daicel Co, Ltd, Japan) eluting with 99% *n*-hexane containing 1% EtOH at 0.5 mL/min. Under these conditions, good separation of each enantiomer was achieved: coronafacic acid methyl ester **17** at Rt = 28.3 min and ***ent*-17** at Rt 25.9 min. Enantiomeric excess was calculated from the ratio of peak areas (mAu s) at 230 nm. Chiral HPLC analysis of 6 ng of the synthetic **17** gave a ratio of **17**: ***ent*-17** = 2328: 8.74, which corresponded to 99.6% ee. According to the above-mentioned procedure, Chiral HPLC analysis of 10 ng of the synthetic ***ent*-17** gave a ratio of **17**: ***ent*-17** = 8.94: 5021, which corresponded to 99.8% ee.

3 | RESULTS AND DISCUSSION

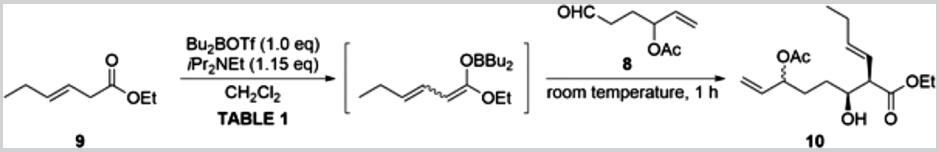
3.1 | Preparation of (±)-coronafacic acid

We first prepared a racemic mixture of (±)-**3** according to Watson's procedure (with modifications to the boron aldol reaction) starting from 26.1 g of 1,4-butanediol **5** (Scheme 1). Mono-THP protection of 1,4-butanediol and Swern oxidation, followed by Grignard reaction with vinyl magnesium bromide and quenching with acetic anhydride gave the acetate **7**. Acidic deprotection of THP group with PPTS in EtOH and subsequent Swern oxidation afforded 4.6 g of aldehyde **8**. The yield of the acidic deprotection step was improved by diluting the reaction solution from 28 to 5 mM (66% to 92%). However, the aldol reaction between aldehyde **8** and ester **9** was problematic and greatly influenced by the time taken to prepare the boron enolate and the temperature (Table 1). We first stirred ester **9** and dibutylboron triflate at room temperature for 30 minutes and then added aldehyde, as described by Watson. Unfortunately, yields of product obtained by this procedure were poorly reproducible (entry 1), presumably due to decomposition of the boron enolate—a consequence of the exothermic nature of the reaction. The *syn/anti* selectivity in boron-mediated aldol reaction highly depends on the reaction temperature. Under the cryogenic conditions, this reaction predominantly affords the *anti*-product.[10] In contrast, the *syn* isomer is predominantly obtained at room temperature.[7,11] Therefore, we planned to carry out the reaction at room temperature to obtain the desired *syn* isomer. However, the preparation of boron enolate at −78°C followed by the addition of **8** having allowed the enolate solution to warm to room temperature did not improve the reproducibility (entry 2). In contrast, the addition of aldehyde **8** immediately after mixing ester **9** and dibutylboron triflate at room temperature dramatically improved yield and reproducibility and slightly improved stereoselectivity (*syn*:*anti* 83:17 to 90:10) (entry 3). This was attributed to the instability of the resulting boron enolate at room temperature.[8] Intramolecular Diels-Alder reaction and subsequent deprotection of the acetyl group afforded the *trans*-hydrindane derivative **11**. Finally, Dess-Martin oxidation and acid hydrolysis with concurrent epimerization of the C7a position gave 2.1 g of racemic (±)-**3** in 36% overall yield.



SCHEME 1 Reagents and conditions: (a) DHP, $AlCl_3$, 98%; (b) $(COCl)_2$, NEt_3, CH_2Cl_2, DMSO, −78°C to rt; (c) CH_2 = $CHMgBr$, THF, −0°C to rt, 96% (2 steps); (d) PPTS, EtOH, 75°C, 92%; (e) $(COCl)_2$, NEt_3, CH_2Cl_2, DMSO, −78°C to rt, 95%; (f) **9**, Bu_2BOTf, iPr_2NEt, CH_2Cl_2, 81% (*syn*:*anti* = 90:10); (g) CuBr, DIC, toluene, reflux; (h) *p*TsOH, EtOH, 75°C, 77% (2 steps); (i) Dess-Martin periodinane, CH_2Cl_2; (j) HCl, reflux, 77% (2 steps)

TABLE 1 Boron-mediated aldol reaction

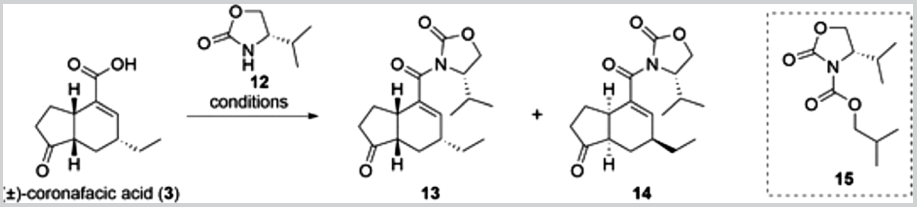


Entry	Temperature	Time	10	*syn*:*anti*
1	rt	30 min	0%-68%	78:22-83:17
2	−78°C	2 h	32%-50%	68:32-83:17
3	rt	3 min	65%-81%	85:15-90:10

3.2 | Optical resolution of (±)-coronafacic acid

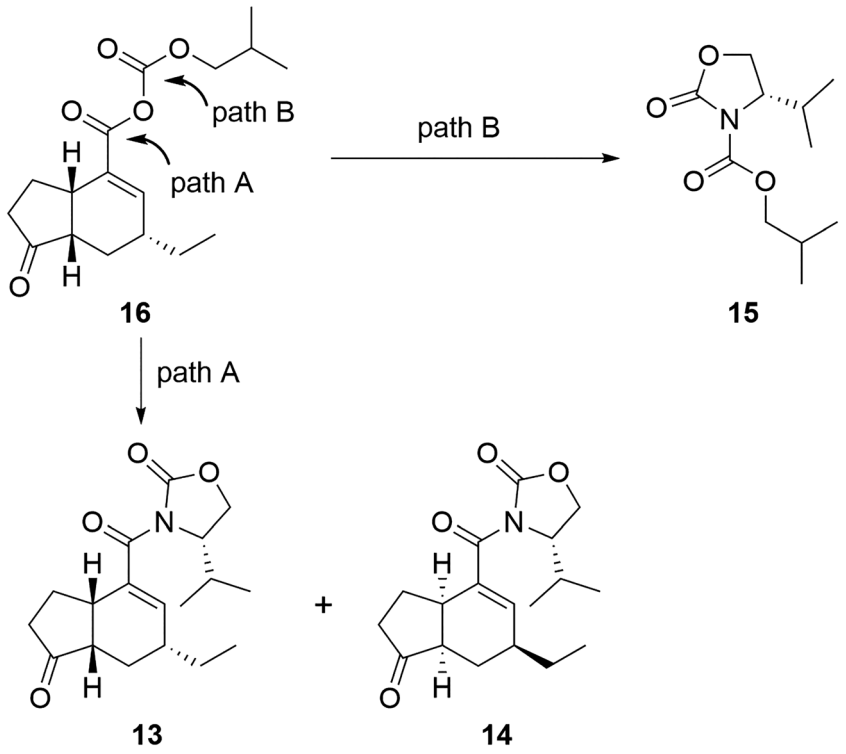
Recently, Miyamoto et al reported a highly practical method for the optical resolution of racemic jasmonic acid using the chiral auxiliary (*S*)-4-isopropyl-2-oxazolidinone (**12**).[12] We applied this method to the optical resolution of racemic (±)-**3**. The coupling of (±)-**3** with **12** was first investigated (Table 2). Using Miyamoto's conditions, the desired coupling products **13** and **14** were obtained, but the yields of coronafacyl oxazolidinones **13** and **14** were low (entry 1) and accompanied by formation of by-product **15**, presumably according to the mechanism depicted in path B of Scheme 2. From this result, we inferred that the use of mixed acid anhydride bearing a bulkier substituent than that of chloroisobutylformate would favor path A (Scheme 2), resulting in a higher yield.

TABLE 2 Optical resolution of racemic coronafacic acid



Entry	Conditions	13	14	15
1	$(CH_3)_2CHCH_2OCOCl$ (2.0 eq), NMM (2.0 eq), THF, rt, 30 min; **12** (1.5 eq), *n*BuLi (1.0 eq), DMAP, −78°C, 23 h	16%	17%	74%[a]
2	PivCl (2.0 eq), NMM (2.0 eq), THF, rt, 2 h; **12** (1.5 eq), *n*BuLi (1.0 eq), DMAP, −78°C, 19 h	30%	33%	—
3	PivCl (1.5 eq), Et_3N (5.3 eq), CH_2Cl_2, rt, 2 h; **12** (2.1 eq), LiCl (3.0 eq), DMAP (0.1 eq), rt, 18 h	49%	48%	—

[a]The yield is based on **12**.



SCHEME 2 Mechanism of the formation of carbamate **15**

Therefore, we attempted the reaction using PivCl instead of chloroisobutylformate (entry 2). The yields of **13** and **14** did improve, but some by-products were nevertheless observed. The reaction yields of the *N*-acylation of oxazolidine-2-ones (via the lithium anion) and α,β-unsaturated acyl acceptors are known to be reduced

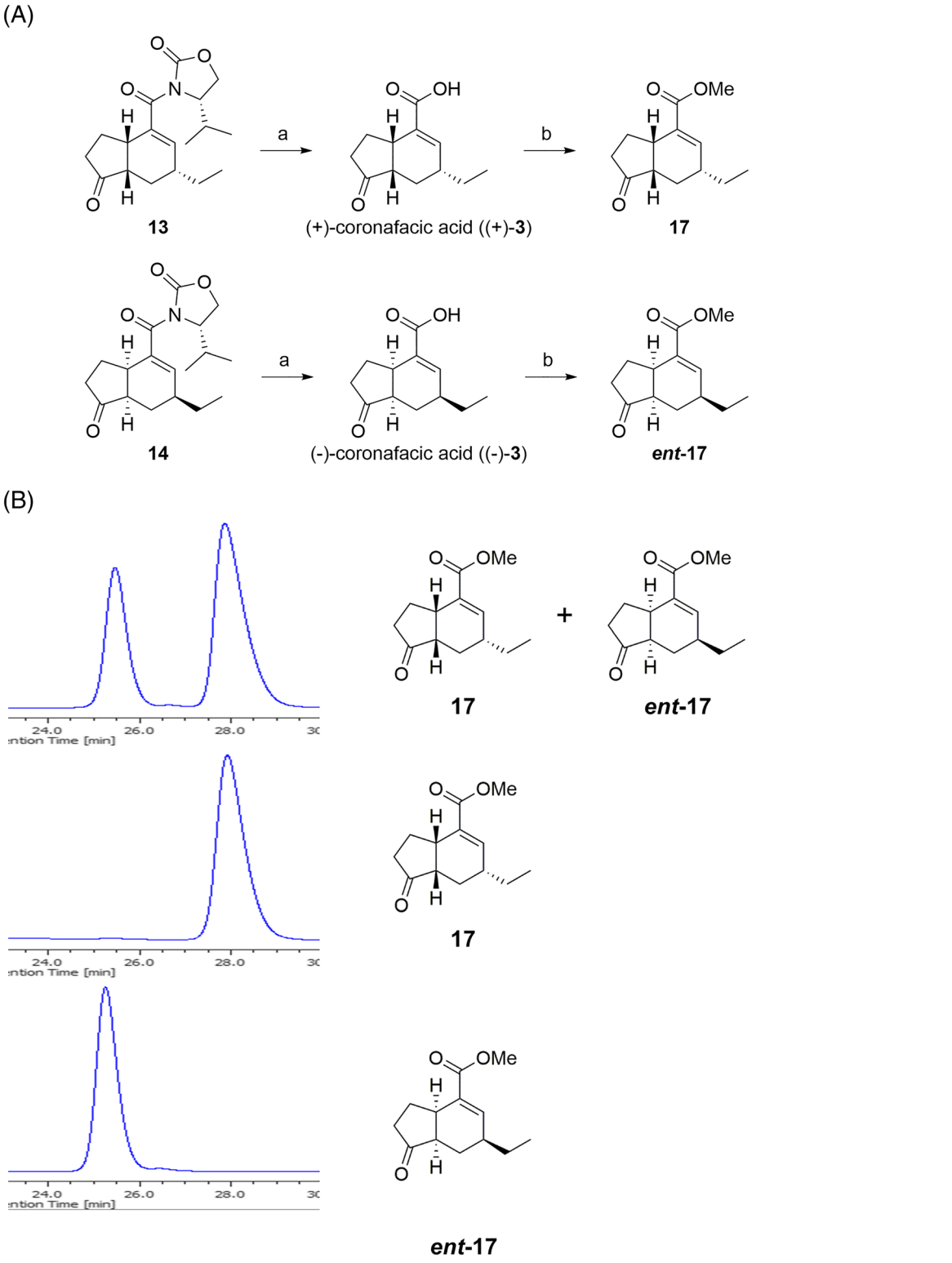


FIGURE 2 A, Reagents and conditions: (a) H_2O_2, LiOH, THF, H_2O, (+)-**3** (89%), (−)-**3** (82%); (b) $TMSCHN_2$, MeOH, benzene, **17** (quant), ***ent*-17** (quant). B, Optical purity of **17** and ***ent*-17**. Optical purities were determined by chiral HPLC analyses on a Chiralpak IA ϕ4.6 × 250 mm column (Daicel Co, Ltd, Japan) (mobile phase: 99% *n*-hexane containing 1% EtOH; flow rate: 0.5 mL/min)

by side reactions such as the conjugate addition of oxazolidine-2-one anions to acyl acceptors.[13] Therefore, we employed a mild procedure with lithium chloride and triethylamine (entry 3).[14] The resulting diastereomer mixture was easily separated by silica gel column chromatography to give **13** and **14** in excellent yields. Samples of both **13** and **14** were separately treated with lithium hydroperoxide to afford 630 mg of optically active (+)-**3** ($[\alpha]^{23}_{D}$ + 121; lit[8] $[\alpha]^{23}_{D}$ + 122) and 580 mg of (−)-**3** ($[\alpha]^{23}_{D}$ − 118), respectively (Figure 2A). The addition of acetic acid to the eluent used during the purification of (+)-**3** and (−)-**3** by silica-gel column chromatography slightly improved their recovery. The optical purities of (+)-**3** and (−)-**3** were determined by chiral HPLC analyses on a Chiralpak IA after methyl esterification with trimethylsilyl diazomethane (Figure 2B). Chiral HPLC analysis of synthetic **17** and ***ent*-17** gave optical purities of >99.5% ee.

4 | CONCLUSION

A facile, efficient, and scalable synthesis of optically pure (+)-**3** and (−)-**3** has been developed. Our method comprises two stages—synthesis of racemic (±)-**3** by an improved version of Watson's method, followed by its resolution using a chiral auxiliary—and has enabled the preparation of more than 600 mg of optically pure (+)-**3**, an important component of (+)-**1**. This study is anticipated to enable the use of (+)-**1**-based synthetic chemical tools for the study of the chemical biology of jasmonate.

ACKNOWLEDGMENTS

This work was supported by a Grant-in-Aid for Scientific Research for MU from MEXT, Japan (nos. 26282207, 17H06407, and 17H00885), for NK (no. 19K06968), Sunbor Grant (NK), JSPS A3 Foresight Program (MU), and JSPS Core-to-Core Program Asian Chemical Biology Initiative (MU).

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SUPPORTING INFORMATION

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How to cite this article: Kato N, Miyagawa S, Nomoto H, Nakayama M, Iwashita M, Ueda M. A scalable synthesis of (+)-coronafacic acid. *Chirality*. 2020;1–8. https://doi.org/10.1002/chir.23172