ORGANIC LETTERS

2011
Vol. 13, No. 16
4232–4235

Synthesis of Coronafacic Acid via TBAF-Assisted Elimination of the Mesylate and Its Conversion to the Isoleucine Conjugate

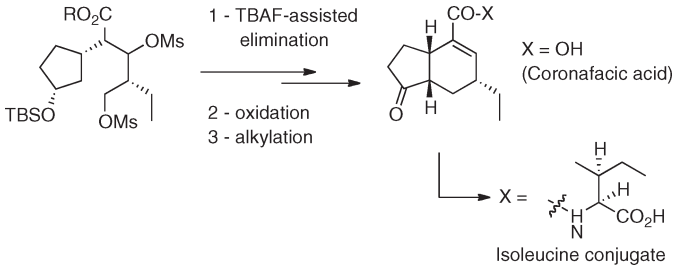
Yusuke Kosaki, Narihito Ogawa, Qian Wang, and Yuichi Kobayashi*

Department of Biomolecular Engineering, Tokyo Institute of Technology, Box B52, Nagatsuta-cho 4259, Midori-ku, Yokohama 226-8501, Japan

ykobayas@bio.titech.ac.jp

Received June 13, 2011

ABSTRACT



An aldol reaction followed by elimination of the derived mesylate was used to construct the side chain that was designed to afford the cyclohexene ring of coronafacic acid via intramolecular alkylation. Elimination of the mesylate proceeded with TBAF. The alkylation was achieved with *t*-BuOK in THF, and then hydrolysis afforded coronafacic acid, which upon condensation with unprotected L-isoleucine using $ClCO_2Bu^i$ furnished coronafacoyl-L-isoleucine, the L-Ile conjugate.

Coronatine **1a** is a phytotoxin isolated from *Pseudomonas syrigae* pv *atropurpurea* as a chlorosis-inducing factor against Italian ryegrass leaves,[1] and biosynthesis of **1a** has been elucidated[2] (Figure 1). Structurally similar compounds such as **1b**–**d** have been found as well.[3] Although it is a phytotoxin, **1a** shows biochemical activities similar to those of some jasmonoids,[4] which regulate plant physiology and defense responses against environmental and pathogenic stressors.[5] Since **1a** is highly potent and chemically more stable than the jasmonoids, **1a** has been utilized as a stable probe to find the coronatine insensitive proteins 1 (COI1 proteins), which are the SCF proteins

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

(2) (a) Parry, R. J.; Mafoti, R. *J. Am. Chem. Soc.* **1986**, *108*, 4681–4682. (b) Parry, R. J.; Lin, M.-T.; Walker, A. E.; Mhaskar, S. *J. Am. Chem. Soc.* **1991**, *113*, 1849–1850.

(3) (a) Young, S. A.; Park, S. K.; Rodgers, C.; Mitchell, R. E.; Bender, C. L. *J. Bacteriol.* **1992**, *174*, 1837–1843. (b) Mitchell, R. E. *Phytochemistry* **1991**, *30*, 3917–3920. (c) Mitchell, R. E.; Frey, E. J. *J. Gen. Microbiol.* **1986**, *132*, 1503–1507. (d) Mitchell, R. E.; Young, H. *Phytochemistry* **1985**, *24*, 2716–2717. (e) Shiraishi, K.; Konoma, K.; Sato, H.; Ichihara, A.; Sakamura, S.; Nishiyama, K.; Sakai, R. *Agric. Biol. Chem.* **1979**, *43*, 1753–1757.

(4) (a) Haider, G.; Von Schrader, T.; Füβlein, M.; Blechert, S.; Kutchan, T. M. *Biol. Chem.* **2000**, *381*, 741–748. (b) Blechert, S.; Bockelmann, C.; Füβlein, M.; Schrader, T. V.; Stelmach, B.; Niesel, U.; Weiler, E. W. *Planta* **1999**, *207*, 470–479.

(5) (a) Chen, H.; McCaig, B. C.; Melotto, M.; He, S. Y.; Howe, G. A. *J. Biol. Chem.* **2004**, *279*, 45998–46007. (b) Staswick, P. E.; Tiryaki, I. *Plant Cell* **2004**, *16*, 2117–2127. (c) Uppalapati, S. R.; Ayoubi, P.; Weng, H.; Palmer, D. A.; Mitchell, R. E.; Jones, W.; Bender, C. L. *Plant J.* **2005**, *42*, 201–217. (d) Wasternack, C. *Ann. Bot.* **2007**, *100*, 681–697. (e) Uppalapati, S. R.; Ishiga, Y.; Wangdi, T.; Kunkel, B. N.; Anand, A.; Mysore, K. S.; Bender, C. L. *Mol. Plant-Microbe Interact.* **2007**, *20*, 955–965. (f) Munemasa, S.; Oda, K.; Watanabe-Sugimoto, M.; Nakamura, Y.; Shimoishi, Y.; Murata, Y. *Plant Physiol.* **2007**, *143*, 1398–1407. (g) Howe, G. A.; Jander, G. *Annu. Rev. Plant Biol.* **2008**, *59*, 41–66. (h) Browse, J. *Annu. Rev. Plant Biol.* **2009**, *60*, 183–205.

(6) Xie, D. X.; Feys, B. F.; James, S.; Nieto-Rostro, M.; Turner, J. G. *Science* **1998**, *280*, 1091–1094.

(7) (a) Thines, B.; Katsir, L.; Melotto, M.; Niu, Y.; Mandaokar, A.; Liu, G.; Nomura, K.; He, S. Y.; Howe, G. A.; Browse, J. *Nature* **2007**, *448*, 661–665. (b) Chini, A.; Fonseca, S.; Fernández, G.; Adie, B.; Chico, J. M.; Lorenzo, O.; García-Casado, G.; López-Vidriero, I.; Lozano, F. M.; Ponce, M. R.; Micol, J. L.; Solano, R. *Nature* **2007**, *448*, 666–671.

(8) (a) Fonseca, S.; Chini, A.; Hamberg, M.; Adie, B.; Porzel, A.; Kramell, R.; Miersch, O.; Wasternack, C.; Solano, R. *Nat. Chem. Biol.* **2009**, *5*, 344–350. (b) Chung, H. S.; Cooke, T. F.; DePew, C. L.; Patel, L. C.; Ogawa, N.; Kobayashi, Y.; Howe, G. A. *Plant J.* **2010**, *63*, 613–622.

10.1021/ol201576c
Published on Web 07/18/2011

targeting the repressor JAZ proteins.[6] Recently, **1a** and *epi*-jasmonoyl-L-isoleucine **4** were found to highly activate COI1 proteins binding to JAZ proteins,[7] whereas jasmonoyl-L-isoleucine, the C7 stereoisomer, was less active.[8] Quite recently, the crystal structure of the complex consisting of **4**, COI1, and JAZ was published.[9] A similar complex with **1a** occupying the site for **4** was also disclosed. The phenyl group of Phe89 is definitely responsible for the stereospecificity of the site to the stereogenic centers on the cyclopentane ring of **4** and **1a** and to the Et group of **1a** as well. To elucidate the mechanism, which translates the binding signals by **1a** and **4** in different ways, a method of conveniently supplying these molecules and analogues should be established. Recently, we succeeded in synthesizing **4** and other amino acid conjugates of *epi*-jasmonic acid **5**.[10] Herein, we report the synthesis of coronafacic acid **2**, the known precursor to **1a**, and its conversion to coronafacoyl-L-isoleucine **1c** under protective group-free conditions.

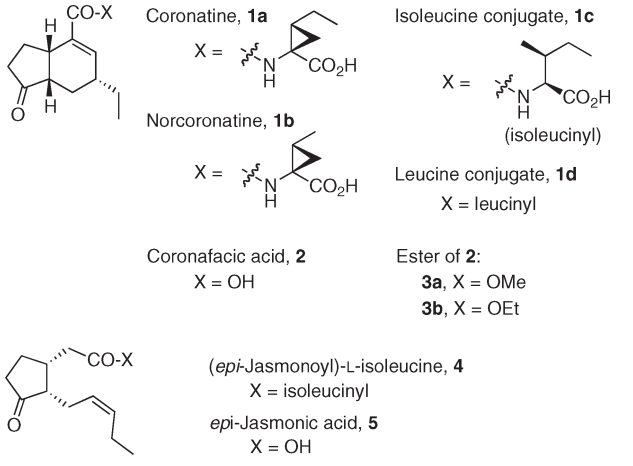


Figure 1. Coronatine, its derivatives, and (*epi*-jasmonoyl)-L-isoleucine.

Since the previous asymmetric syntheses of **2**[11,12] suffer from low selectivity, we focused our attention mainly on stereoselective construction of the C6 stereogenic center possessing the Et group and total yield. In our preliminary experiments (Figure 2), each pair of keto esters (**3a** and **3a′**) and hydroxyl esters (**6a** and **6a′**) was nearly coeluted on TLC (hexane/EtOAc) (synthesis not shown). In consideration of the close mobility between the diastereomers we envisaged a synthesis of **2** through aldol reaction of **8** with aldehyde **9** followed by elimination of the derived mesylate **7** and intramolecular alkylation (Scheme 1). As described below, the elimination proceeded under unexpected conditions and, besides, with the desired (*E*)-stereoselectivity. The ester **8** for the aldol reaction was expected to be obtained through palladium-catalyzed allylic substitution of the corresponding acetate[13] with malonate, while aldehyde **9** was prepared according to the literature method.[14]

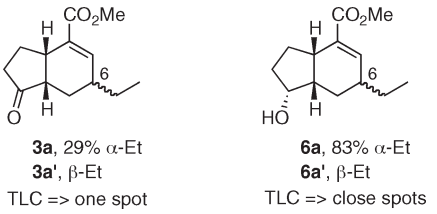
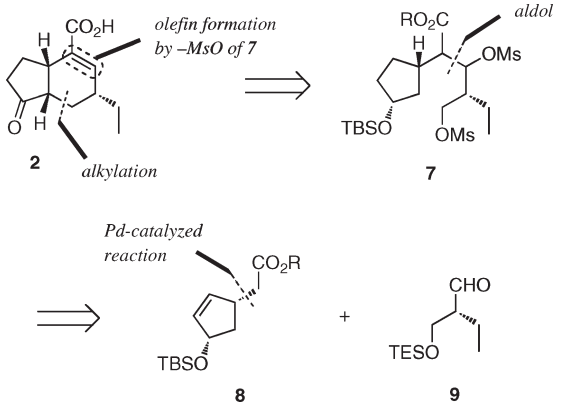


Figure 2. TLC mobility of the two sets of the diastereomeric mixtures.

Scheme 1. Retrosynthesis of Coronafacic Acid



As summarized in Scheme 2 the TBS-protected acetate **11**, derived from monoacetate **10**[13] with 99% ee, was subjected to the palladium-catalyzed allylic substitution with methyl malonate **12a** according to the method published by us[15] to produce **13a**, which upon decarboxylation with KI at 140 °C afforded ester **8a** in 81% yield from **11**.

(9) Sheard, L. B.; Tan, X.; Mao, H.; Withers, J.; Ben-Nissan, G.; Hinds, T. R.; Kobayashi, Y.; Hsu, F.-F.; Sharon, M.; Browse, J.; He, S. Y.; Rizo, J.; Howe, G. A.; Zheng, N. *Nature* **2010**, *468*, 400–405.

(10) Ogawa, N.; Kobayashi, Y. *Amino Acids* **2011**, DOI: 10.1007/s00726-011-0925-z.

(11) (a) Taber, D. F.; Sheth, R. B.; Tian, W. *J. Org. Chem.* **2009**, *74*, 2433–2437. (b) Mehta, G.; Reddy, D. S. *J. Chem. Soc., Perkin Trans. 1* **2001**, 1153–1161. (c) Arai, T.; Sasai, H.; Yamaguchi, K.; Shibasaki, M. *J. Am. Chem. Soc.* **1998**, *120*, 441–442. (d) Nara, S.; Toshima, H.; Ichihara, A. *Tetrahedron* **1997**, *53*, 9509–9524. (e) Toshima, H.; Nara, S.; Ichihara, A. *Biosci. Biotech. Biochem.* **1997**, *61*, 752–753. (f) Ohira, S. *Bull. Chem. Soc. Jpn.* **1984**, *57*, 1902–1907. (g) Nakayama, M.; Ohira, S. *Agric. Biol. Chem.* **1983**, *47*, 1689–1690.

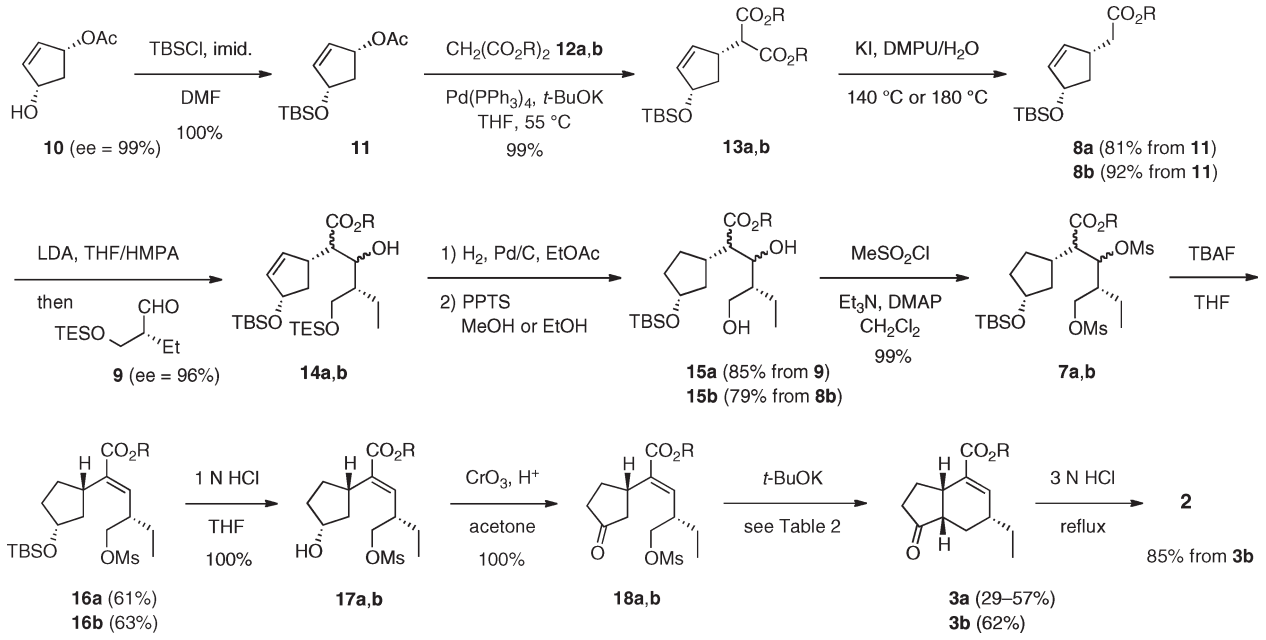
(12) Cf. Recent synthesis in a racemic form: (a) Moreau, B.; Ginisty, M.; Alberico, D.; Charette, A. B. *J. Org. Chem.* **2007**, *72*, 1235–1240. (b) Okada, M.; Egoshi, S.; Ueda, M. *Biosci. Biotechnol. Biochem.* **2010**, *74*, 2092–2095. (c) Okada, M.; Ito, S.; Matsubara, A.; Iwakura, I.; Egoshi, S.; Ueda, M. *Org. Biomol. Chem.* **2009**, *7*, 3065–3073. (d) Sono, M.; Hashimoto, A.; Nakashima, K.; Tori, M. *Tetrahedron Lett.* **2000**, *41*, 5115–5118.

(13) (a) Sugai, T.; Mori, K. *Synthesis* **1988**, 19–22. (b) Laumen, K.; Schneider, M. P. *J. Chem. Soc., Chem. Commun.* **1986**, 1298–1299. (c) Curran, T. T.; Hay, D. A.; Koegel, C. P. *Tetrahedron* **1997**, *53*, 1983–2004.

(14) Osorio-Lozada, A.; Olivo, H. F. *J. Org. Chem.* **2009**, *74*, 1360–1363.

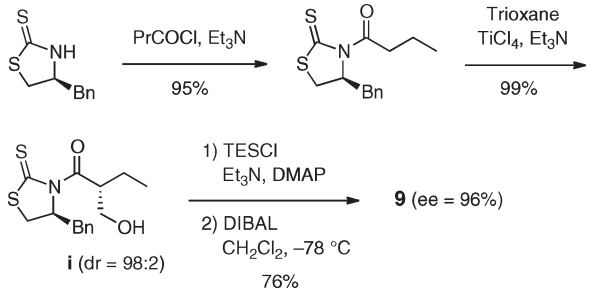
(15) Acharya, H. P.; Kobayashi, Y. *Tetrahedron* **2006**, *62*, 3329–3343.

Scheme 2. Synthesis of Coronafacic Acid (**a** series, R = Me; **b** series, R = Et)



The next stage was aldol reaction followed by elimination of the hydroxyl group to afford the (*E*)-olefin, which was expected to be derived from the *syn* aldol isomer on the basis of well-accepted *anti* elimination. With the above consideration in mind aldol reaction of **8a** with aldehyde **9** (96% ee),[16] prepared by the literature method,[14] was attempted under the *syn* selective conditions using Bu_2BOTf and *i*-Pr_2NEt.[17,12a] However, no reaction took place, suggesting the cyclopentene ring of **8a** being a big obstacle. On the other hand, aldol reaction of lithium enolate[18] derived from **8a** in THF/HMPA (4:1) with **9** afforded **14a** as a mixture of the *syn*/*anti* stereoisomers (four isomers).[19] Note that boron-mediated aldol reaction of model ester **19** with achiral aldehyde **20** afforded **21** stereoselectively (Scheme 3, eq 1), whereas another set of aldol reactions (real ester **8a** and **20**) was unsuccessful.

(16) Prepared as shown below. Enantiomeric excess (ee) of **9** was calculated from the diastereomeric ratio of the intermediate **i**. Yields and diastereoselectivity were comparable with those in the literature.[14]

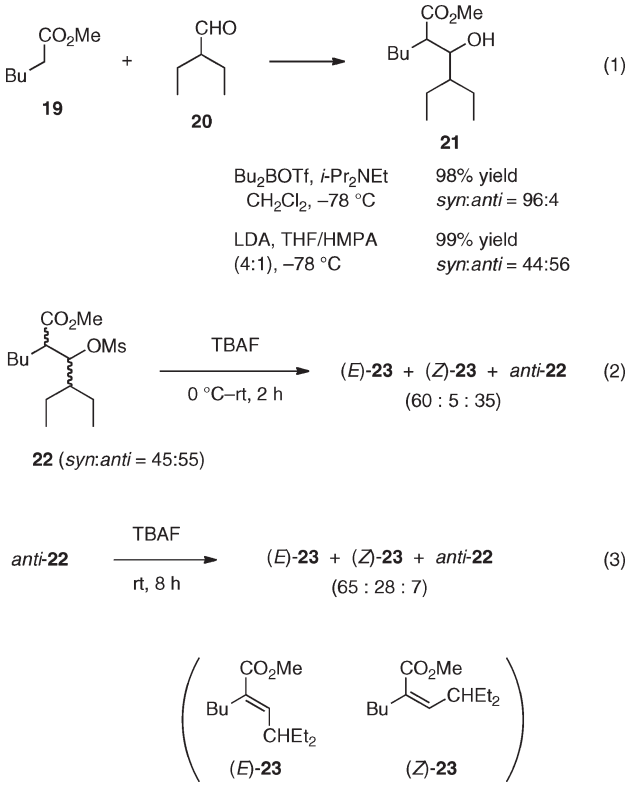


(17) Inoue, T.; Liu, J.-F.; Buske, D. C.; Abiko, A. *J. Org. Chem.* **2002**, *67*, 5250–5256.

(18) (a) Mondal, S.; Malik, C. K.; Ghosh, S. *Tetrahedron Lett.* **2008**, *49*, 5649–5651. (b) Heathcock, C. H.; Buse, C. T.; Kleschick, W. A.; Pirrung, M. C.; Sohn, J. E.; Lampe, J. *J. Org. Chem.* **1980**, *45*, 1066–1081. (c) Meyers, A. I.; Reider, P. J. *J. Am. Chem. Soc.* **1979**, *101*, 2501–2502. (d) See ref 11d.

(19) Multiplicity of the resonances in the ^1H NMR spectrum prevented calculation of a *syn*/*anti* ratio and assignment of the signals to the *syn* and *anti* isomers by coupling constants.

Scheme 3. Model Study of Aldol Reaction (eq 1) and Elimination (eqs 2, 3)



Without determination of the *syn*/*anti* ratio, aldol **14a** was converted to diol **15a** and then to mesylate **7a** in a good yield. Next, desilylation of mesylate **7a** was attempted with TBAF (1.2 equiv) in THF at 0 °C to rt for 2 h. To our surprise, no desilylation took place. Instead, elimination of the mesyloxy group proceeded to furnish **16a** in 61% yield with 90% (*E*)-selectivity over the (*Z*)-isomer as a consequence of deprotonation at the α-position of the ester group.[20] The reagents (Et_3N, Al_2O_3,[15,21] and DBU[22]) used for elimination of the mesylates derived from ketone aldols afforded the olefin marginally.

To understand the selective formation of (*E*)-olefin from the *syn*/*anti* mixture of aldol **14a**, the model mesylate **22** (*syn*/*anti* = 45:55), synthesized by aldol reaction of the lithium enolate of **19** with **20** (Scheme 3, eq 1) followed by mesylation, was treated with TBAF under similar conditions (0 °C−rt, 2 h) to afford a mixture of (*E*)-**23**, (*Z*)-**23**, and *anti*-**22** in a 60:5:35 ratio by ^{1}H NMR spectroscopy. The product was fractionalized by chromatography to give a mixture of (*E*)- and (*Z*)-**23** in 55% yield and *anti*-**22** in 33% yield. The result indicates that *anti* elimination of *anti*-**22**, which should afford (*Z*)-**23**, was retarded by the steric repulsion between the Bu and $CHEt_2$ groups in the transition state, whereas *anti* elimination of *syn*-isomer **22** took place without difficulty. In accord with the result, unusual *syn* elimination of the recovered *anti*-**22** started at rt slowly to afford, after 8 h, a mixture of (*E*)-**23**, (*Z*)-**23**, and *anti*-**22** in a ratio given in eq 3.

The TBS group in **16a** was removed under acidic conditions, and the resulting alcohol **17a** was oxidized to ketone **18a**, which was subjected to intramolecular alkylation with *t*-BuOK as a base. In THF at 0 °C, **3a** was produced with unidentified polar products and an isolated yield of **3a** was only 31% (Table 1, entry 1). The polar compounds were produced even at lower temperature (entry 2). Sufficiently protic conditions were examined next using *t*-BuOH as a solvent at rt due to the mp of *t*-BuOH (entry 3). The reaction was, however, capricious producing 29−57% yields of **3a**. Use of *t*-BuOH/THF (1:1) at 0 °C was unsuccessful (entry 4).

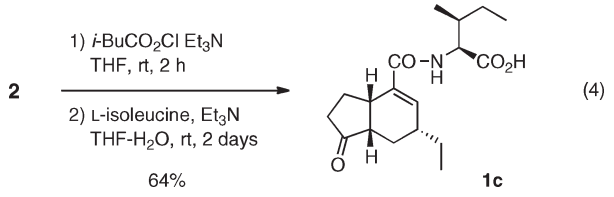
Based on the assumption that attack to the ester carbonyl group in **18a** and/or **3a** was responsible for the formation of polar compounds, intramolecular alkylation of **18b** with the slightly bigger ethyl ester was examined next. Synthesis was accomplished in a similar way to methyl ester **18a** starting with acetate **10** and ethyl malonate **12b** as summarized in Scheme 2. Except for decarboxylation of **13b**, which was accomplished at 180 °C, the other steps of transformation including stereoselective elimination of mesylate **7b** to olefin **16b**[20] proceeded without any event. Intramolecular alkylation of **18b** was carried out with *t*-BuOK in THF at 0 °C to afford **3b** in a higher yield of 62% (Table 1, entry 5). Finally, hydrolysis of **3b** under the reported acidic conditions afforded coronafacic acid **2** in 85% yield. The ^{1}H and ^{13}C NMR spectra and mp were consistent with those reported (see Supporting Information).[23]

Table 1. Intramolecular Alkylation Using *t*-BuOK

entry	ketone	conditions[a]	yield[b]
1	**18a**	THF, 0 °C	31%
2	**18a**	THF, −20 °C	23%
3	**18a**	*t*-BuOH, rt	29%−57%
4	**18a**	*t*-BuOH/THF,[c] 0 °C	27%
5	**18b**	THF, 0 °C	62%

[a] *t*-BuOK (1.2−2.0 equiv). [b] Isolated yield. [c] 1:1.

Finally, coronafacic acid **2** was transformed successfully to coronafacoyl-L-isoleucine **1c** with unprotected L-isoleucine as shown in eq 4 by using the method recently developed for condensation of *epi*-jasmonic acid with amino acids.[10] This method would be applicable to condensation of **2** and its analogues with other amino acids.



(4)

In summary, we achieved stereoselective synthesis of coronafacic acid **2**, the known key intermediate for synthesis of coronatine **1a**, through intramolecular cyclization of **18b** to **3b**. The total yield from **10** to **2** was 23.9% in 12 steps. During the synthesis we found TBAF-assisted elimination of the mesyloxy group in mesylate **7b**, which proceeded stereoselectively and faster than desilylation of the TBS group in it, furnished the desired (*E*)-olefin **16b**. Furthermore, condensation of **2** and unprotected L-isoleucine were achieved successfully to afford the isoleucine conjugate **1c**.

Acknowledgment. This work was supported by a Grant-in-Aid for Scientific Research from the Ministry of Education, Science, Sports, and Culture, Japan.

Supporting Information Available. Experimental procedures and spectral data of compounds described herein. This material is available free of charge via the Internet at http://pubs.acs.org.

(20) Chemical shifts (δ, ppm) of the diagnostic olefin proton appeared as a doublet (*J* = ca. 10 Hz): **16a**, 6.33; the (*Z*)-isomer of **16a**, 5.59; **16b**, 6.27; the (*Z*)-isomer of **16b**, 5.51.

(21) Kobayashi, Y.; Murugesh, M. G.; Nakano, M.; Takahisa, E.; Usmani, S. B.; Ainai, T. *J. Org. Chem.* **2002**, *67*, 7110–7123.

(22) In the case of an aldol derived from ester and α,β-enal, elimination of the derived mesylate proceeds with DBU.[11d] A similar tendency was observed by us.[15]

(23) The specific rotations ($[\alpha]_D$) in MeOH reported earlier are ca. 120, whereas those reported recently are 104−109. Our data are consistent with the latter. See Supporting Information.