Organic LETTERS
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Practical Total Syntheses of Acromelic Acids A and B

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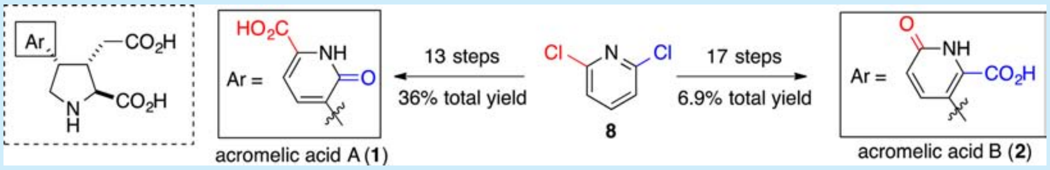
Supporting Information



ABSTRACT: Practical total syntheses of acromelic acids A (**1**) and B (**2**), which have potent neuro-excitatory activity, were accomplished in 13 (36% total yield) and 17 steps (6.9% total yield), respectively, from 2,6-dichloropyridine (**8**). Regioselective transformation of symmetric **8** provided nitroalkenes **15** and **16**. The pyrrolidine ring was efficiently constructed by Ni-catalyzed asymmetric conjugate addition followed by intramolecular reductive amination.

In 1983, Shirahama and Matsumoto isolated 110 μg and 40 μg of acromelic acids A (**1**) and B (**2**) (Figure 1), respectively, from 16 kg of Clitocybe acromelalga (Japanese name, dokusasako) and determined their structures by means of extensive NMR analysis[1] and total syntheses.[2] These amino acids exhibit remarkably potent neuro-excitatory activity via activation of ionotropic glutamate receptors in the brain.

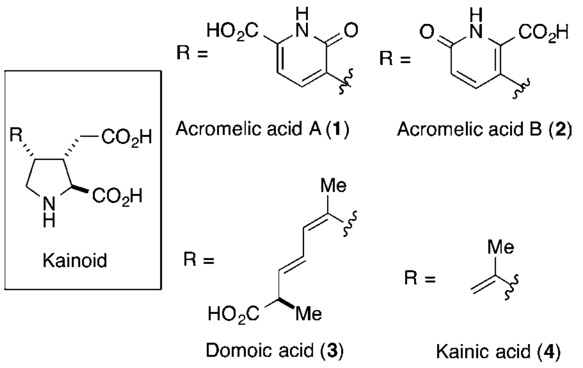


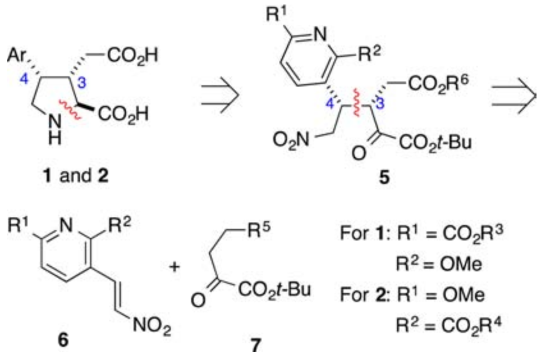
Figure 1. Structures of natural kainoids **1**, **2**, **3**, and **4**.

Compound **1**, for example, is almost 10 times more potent than domoic acid (**3**) and 100 times more potent than kainic acid (**4**).[3] Thus, these compounds have the potential to be important biological research tools, because ionotropic glutamate receptors are involved in various neurophysiological processes, including memory and pain transmission. Allodynia induced by **1** is of interest because of its association with neuropathic pain transmission, but poor availability of **1** meant that recent biological investigations had to be performed with only simple synthetic analogues of **1**.[4]

To date, numerous total syntheses of **4** have been reported,[5] but there are only a few reports of the total synthesis of **1**[6] and **2**.[7] In general, it is preferable to install polar and unstable heterocycles at a late stage during a total synthesis. Indeed, in the early syntheses, the relatively unstable pyridone ring was constructed from a methylpyridine unit,[2,6] so that the difficulty in handling the compounds could be minimized. However, oxidative transformations with toxic heavy metal reagents had to be performed at the final stage, and these syntheses are unsuitable for providing sufficient amounts for detailed biological studies. In contrast, we planned to use methoxypicolinic acid ester as a pyridone precursor to improve the efficiency of the syntheses, even though the reaction of a pyridine substrate might be challenging, since such heterocyclic compounds tend to affect key catalytic and stereoselective reactions. As a part of our research program on kainoid chemistry,[8] we herein describe practical, scaleable total syntheses of acromelic acids A (**1**) and B (**2**).

The heart of our synthetic strategy is shown in Scheme 1, in which substrates with the same oxidation state as the natural

Scheme 1. Synthetic Strategy for Acromelic Acids A and B (1 and 2)



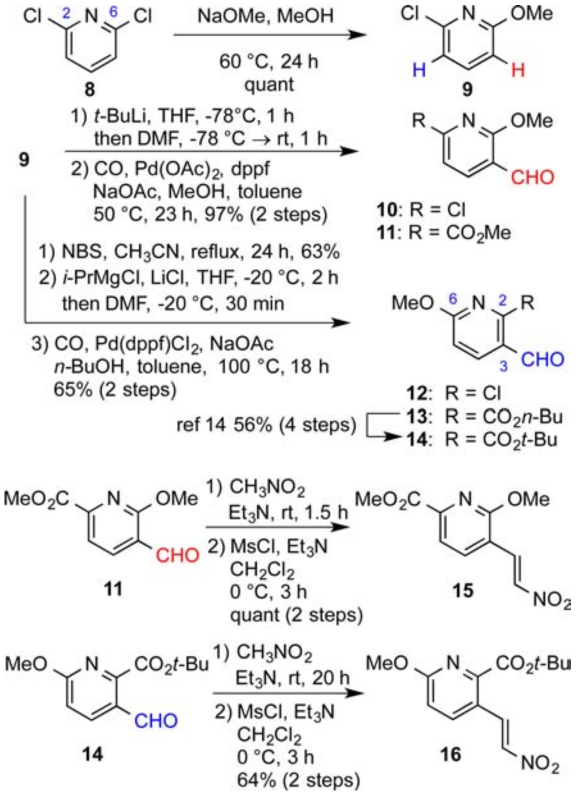
Received: February 18, 2014
Published: March 24, 2014

ACS Publications

products serve as key intermediates. The pyrrolidine ring would be formed from δ-keto-nitro compound **5** via intramolecular reductive amination. Thus, a crucial step of the total synthesis would be stereoselective coupling between nitroalkene **6** and α-ketoester **7**, which we expected to achieve by the use of a Ni-catalyzed asymmetric reaction.[8a] Nitroalkene **6** would be synthesized from the corresponding pyridylaldehyde and nitromethane via Henry reaction and subsequent dehydration. Since **1** and **2** differ only in the substitution pattern on the pyridone ring, the divergent synthesis of both regioisomeric pyridylaldehydes from the same compound is another key feature of the total synthesis.

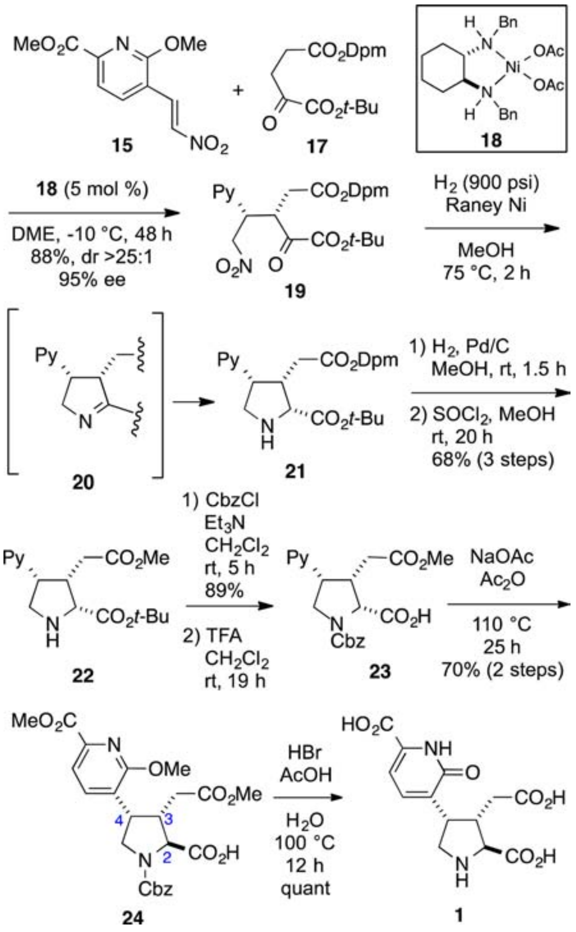
As shown in Scheme 2, aldehyde precursors **11** and **14** could be readily prepared in a divergent manner from inexpensive 2,6-dichloropyridine (**8**). Monosubstitution of **8** with sodium methoxide proceeded smoothly to give 2-chloro-6-methoxypyridine (**9**) in high yield. For the preparation of aldehyde **11**, regioselective introduction of a formyl group was achieved via directed ortho-lithiation[9] followed by a reaction with DMF to give **10**. The carbonylation reaction[10] of **10** proceeded smoothly in the presence of a catalytic amount of Pd(OAc)$_2$−DPPF and methanol under a CO atmosphere to afford the desired aldehyde **11**. On the other hand, bromination of **9** with NBS occurred regioselectively at the para-position of the methoxy group to give a 3-bromopyridine derivative.[11] The corresponding aldehyde **12** was obtained from the bromide according to Knochel's protocol.[12] Incorporation of an ester group into **12** was also accomplished by a Pd-catalyzed carbonylation reaction to provide **13**. Since the n-butyl ester of **13** was reactive in the following transformations,[13] conversion to the bulky *tert*-butyl ester **14** was performed via a four-step sequence.[14] The coupling of aldehyde **11** or **14** with nitromethane, followed by dehydration, provided the nitroalkenes **15** and **16** in high yield, respectively.

Scheme 2. Preparation of Nitro Olefins 15 and 16



For the synthesis of acromelic acid A (**1**), we next investigated the key step needed to construct the vicinal stereocenters at the C-3,4 positions. Fortunately, the asymmetric conjugate addition of nitroalkene **15** with α-ketoester **17** proceeded smoothly in the presence of 5 mol % of Ni(OAc)$_2$−diamine catalyst **18** (Scheme 3). Although we had thought that the presence of the pyridine ring might decelerate the catalysis, the reaction reached completion to give the desired coupling product **19** with the correct stereochemistry in high yield with excellent stereoselectivity (dr = >25:1, 95% ee for the major isomer). The choice of a Dpm (diphenylmethyl) ester was important to achieve excellent diastereoselectivity. As the size of the ester group at the δ-position of the nucleophile was increased, higher diastereoselectivity was observed, probably because epimerization at the α-position of the keto group was minimized.[15] It is noteworthy that this reaction could be carried out on a large scale (10 g scale) without difficulty.

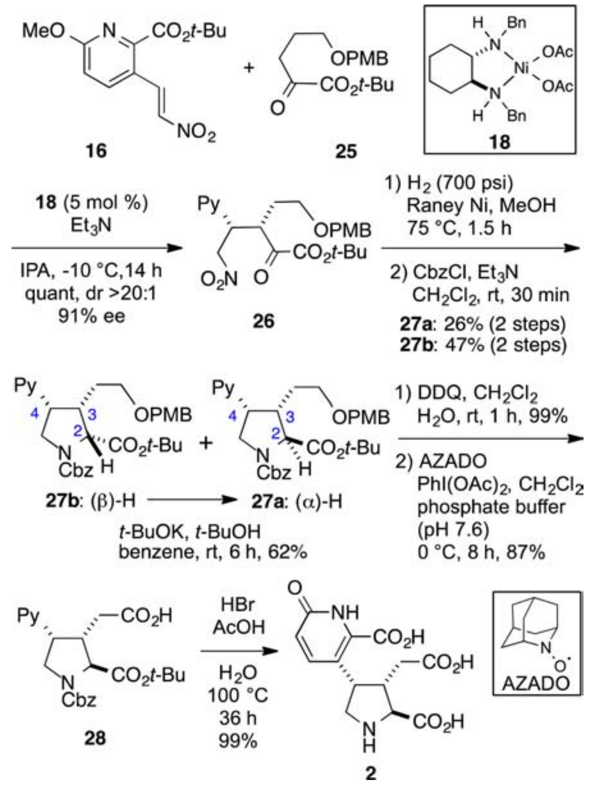
Scheme 3. Completion of Total Synthesis of Acromelic Acid A (1)



With the key intermediate in hand, we next examined the formation of the pyrrolidine ring. Upon treatment of **19** with Raney Ni under 900 psi of hydrogen, reduction of the nitro group, intramolecular condensation with the ketone, and reduction of the resulting ketimine could be performed in a single operation, and the desired pyrrolidine compound **21** was obtained in high yield. The next task was inversion of the stereochemistry at the C-2 position. Treatment of **21** with *t*-BuOK resulted in marked decomposition of the substrate.[16] In order to generate the active ester derivative, conversion of **21** to carboxylic acid **23** was performed via a four-step sequence.[17] Upon treatment with NaOAc in Ac_2O, **23** underwent complete epimerization to give **24** by way of the formation of a mixed anhydride. Finally, simultaneous removal of the Cbz group and the methyl ether on the pyridine ring and concomitant hydrolysis of the methyl esters were carried out by treatment with HBr in acetic acid to provide acromelic acid A (**1**), which gave spectral data (^{1}H NMR, ^{13}C NMR, IR, and HRMS) in full agreement with those of the natural product.[1,2] Thus, the total synthesis of **1** has been accomplished in 13 steps from 2,6-dichloropyridine (**8**) in 36% total yield.

We envisaged that the established route to **1** would also be applicable to acromelic acid B (**2**) (Scheme 4). In the case of **16** as a Michael acceptor, however, the reaction of **17** gave an almost 1:1 mixture of the diastereoisomers, which might be attributed to epimerization during the reaction. To address this issue, we next examined the reaction of α-ketoester **25**. The Ni-catalyzed reaction between **16** and **25** produced the desired product **26** quantitatively with excellent stereoselectivity (dr = 20:1, 91% ee). Subsequent hydrogenation with Raney Ni also proceeded smoothly, but a 1:2 mixture of **27a** and **27b** was isolated after incorporation of a Cbz group at the secondary amine. In contrast to **21**, epimerization from **27b** to **27a** could be performed by treatment with *t*-BuOK in *t*-BuOH.[16] After removal of the PMB (*p*-methoxybenzyl) group, direct conversion of the resulting primary alcohol to the corresponding acid **28** was achieved by Iwabuchi oxidation.[18] Finally, treatment with HBr in acetic acid enabled simultaneous cleavage of the remaining protecting groups to furnish acromelic acid B (**2**). All the spectroscopic data for the synthetic **2** were in good agreement with those of the natural product.[1,2] Thus, the total synthesis of **2** has been accomplished in 17 steps from 2,6-dichloropyridine (**8**) in 6.9% total yield.

Scheme 4. Completion of Total Synthesis of Acromelic Acid B (2)



In conclusion, we have developed practical total syntheses of acromelic acids A and B (**1** and **2**). Our syntheses feature a regioselective synthesis of the methoxypicolinic acid derivatives **11** and **14** from 2,6-dichloropyridine (**8**), efficient construction of the pyrrolidine rings via a sequence involving our asymmetric conjugate addition, intramolecular reductive amination under hydrogenolysis conditions, and basic epimerization of the C-2 position. Our approach is suitable for the large-scale synthesis of **1** and **2**, in amounts sufficient for detailed biological studies. The biological activities of these compounds in mice and the binding behavior to glutamate receptors are under investigation.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Experimental details and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This work was financially supported by a grant from the Uehara Memorial Foundation (to Y.H.), MEXT/JSPS KAKENHI Grant Number 23390007, Grants-in-Aid for Scientific Research on Priority Areas 12045232 and 24105530 from the Ministry of Education, Culture, Sports, Science and Technology (MEXT) of Japan, and a grant for Platform for Drug Discovery, Informatics, and Structural Life Science from the Ministry of Education, Culture, Sports, Science and Technology. We also thank Prof. Mikiko Sodeoka of RIKEN for generous support.

■ REFERENCES

(1) Konno, K.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1983**, *24*, 939−942.

(2) (a) Konno, K.; Hashimoto, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *Tetrahedron Lett.* **1986**, *27*, 607−610. (b) Hashimoto, K.; Konno, K.; Shirahama, H.; Matsumoto, T. *Chem. Lett.* **1986**, 1399−1400. (c) Konno, K.; Hashimoto, K.; Ohfune, Y.; Shirahama, H.; Matsumoto, T. *J. Am. Chem. Soc.* **1988**, *110*, 4807−4815.

(3) (a) Shinozaki, H.; Ishida, M.; Okamoto, T. *Brain Res.* **1986**, *399*, 395−398. (b) Maruyama, M.; Takeda, K. *Brain Res.* **1989**, *504*, 328−331. (c) Shinozaki, H.; Ishida, M.; Kwak, S.; Nakajima, T. *Methods in Neuroscience, Vol. 7: Lesions and Transplantation*, Conn, P. M., Ed.; Academic Press: 1991; pp 38−57.

(4) (a) Miyazaki, S.; Minami, T.; Mizuma, H.; Kanazawa, M.; Doi, H.; Matsumura, S.; Lu, J.; Onoe, H.; Furuta, K.; Suzuki, M.; Ito, S. *Eur. J. Pharmacol.* **2013**, *710*, 120−127. (b) Kanazawa, M.; Furuta, K.; Doi, H.; Mori, T.; Minami, T.; Ito, S.; Suzuki, M. *Bioorg. Med. Chem. Lett.* **2011**, *21*, 2017−2020. (c) Soen, M.; Minami, T.; Tatsumi, S.; Mabuchi, T.; Furuta, K.; Maeda, M.; Suzuki, M.; Ito, S. *Eur. J. Pharmacol.* **2007**, *575*, 75−81.

(5) For recent examples of the enantioselective total synthesis of kainic acid, see: (a) Reddy, N. K.; Chandrasekhar, S. *J. Org. Chem.*

2013, *78*, 3355−3360. (b) Yu, H.-J.; Shao, C.; Cui, Z.; Feng, C.-G.; Lin, G.-Q. *Chem.—Eur. J.* **2012**, *18*, 13274−13278. (c) Kitamoto, K.; Nakayama, Y.; Sampei, M.; Ichiki, M.; Furuya, N.; Sato, T.; Chida, N. *Eur. J. Org. Chem.* **2012**, *22*, 4217−4231. (d) Luo, Z.; Zhou, B.; Li, Y. *Org. Lett.* **2012**, *14*, 2540−2543. (e) Orellana, A.; Pandey, S. K.; Carret, S.; Greene, A. E.; Poisson, J.-F. *J. Org. Chem.* **2012**, *77*, 5286−5296. (f) Evans, P. A.; Inglesby, P. A. *J. Am. Chem. Soc.* **2012**, *134*, 3635−3638. (g) Takita, S.; Yokoshima, S.; Fukuyama, T. *Synthesis* **2011**, 3848−3858. (h) Farwick, A.; Engelhart, J. U.; Tverskoy, O.; Welter, C.; Umlauf, Q. A.; Rominger, F.; Kerr, W. J.; Helmchen, G. *Adv. Synth. Catal.* **2011**, *353*, 349−370. (i) Parsons, P. J.; Rushton, S. P. G.; Panta, R. R.; Murray, A. J.; Coles, M. P.; Lai, J. *Tetrahedron* **2011**, *67*, 10267−10273. (j) Lowe, M. A.; Ostovar, M.; Ferrini, S.; Chen, C. C.; Lawrence, P. G.; Fontana, F.; Calabrese, A. A.; Aggarwal, V. K. *Angew. Chem., Int. Ed.* **2011**, *50*, 6370−6374. (k) Wei, G.; Chalker, J. M.; Cohen, T. *J. Org. Chem.* **2011**, *76*, 7912−7917. (l) Lemière, G.; Sedehizadeh, S.; Toueg, J.; Fleary-Roberts, N.; Clayden, J. *Chem. Commun.* **2011**, *47*, 3745−3747. (m) Takita, S.; Yokoshima, S.; Fukuyama, T. *Org. Lett.* **2011**, *13*, 2068−2070. (n) Kitamoto, K.; Sampei, M.; Nakayama, Y.; Sato, T.; Chida, N. *Org. Lett.* **2010**, *12*, 5756−5759. (o) Farwick, A.; Helmchen, G. *Org. Lett.* **2010**, *12*, 1108−1111. (p) Tomooka, K.; Akiyama, T.; Man, P.; Suzuki, M. *Tetrahedron Lett.* **2008**, *49*, 6327−6329. (q) Sakaguchi, H.; Tokuyama, H.; Fukuyama, T. *Org. Lett.* **2008**, *10*, 1711−1714. For a review of kainoids synthesis: (r) Parsons, A. F. *Tetrahedron* **1996**, *52*, 4149−4174. (s) Wood, M. E.; Fryer, A. M. *Advances in Nitrogen Heterocycles* **1998**, *3*, 159−218. (t) Stathakis, C. I.; Yioti, E. G.; Gallos, J. K. *Eur. J. Org. Chem.* **2012**, *25*, 4661−4673.

(6) Total synthesis of **1** other than that in ref 2: (a) Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J.; Spyvee, M. R.; Whitehead, R. C.; Wood, M. E. *Tetrahedron* **1998**, *54*, 7465−7484. (b) Baldwin, J. E.; Fryer, A. M.; Pritchard, G. J.; Spyvee, M. R.; Whitehead, R. C.; Wood, M. E. *Tetrahedron Lett.* **1998**, *39*, 707−710. (c) Baldwin, J. E.; Li, C. S. *J. Chem. Soc., Chem. Commun.* **1988**, *4*, 261−263. (d) Takano, S.; Iwabuchi, Y.; Ogasawara, K. *J. Am. Chem. Soc.* **1987**, *109*, 5523−5524.

(7) Total synthesis of **2** other than ref 2: (a) Horikawa, M.; Hashimoto, K.; Shirahama, H. *Tetrahedron Lett.* **1993**, *34*, 331−334. (b) Takano, S.; Tomita, S.; Iwabuchi, Y.; Ogasawara, K. *Heterocycles* **1989**, *29*, 1473−1476.

(8) (a) Nakamura, A.; Lectard, S.; Hashizume, D.; Hamashima, Y.; Sodeoka, M. *J. Am. Chem. Soc.* **2010**, *132*, 4036−4037. (b) Higashi, T.; Isobe, Y.; Ouchi, H.; Suzuki, H.; Okazaki, Y.; Asakawa, T.; Furuta, T.; Wakimoto, T.; Kan, T. *Org. Lett.* **2011**, *13*, 1089−1091.

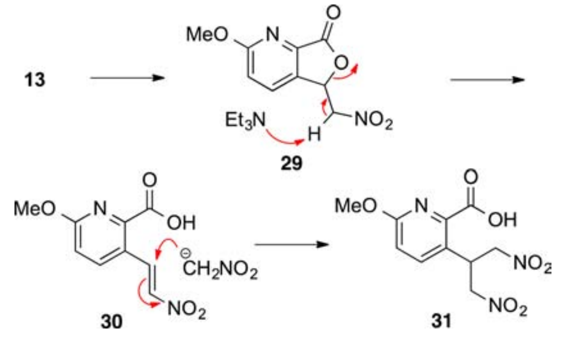
(9) Snieckus, V. *Chem. Rev.* **1990**, *90*, 879−933.

(10) Barnard, C. F. J. *Organometallics* **2008**, *27*, 5402−5422.

(11) Cañibano, V.; Rodríguez, J. F.; Santos, M.; Sanz-Tejedor, M. A.; Carreño, M. C.; González, G.; García-Ruano, J. L. *Synthesis* **2001**, 2175−2179.

(12) Krasovskiy, A.; Knochel, P. *Angew. Chem., Int. Ed.* **2004**, *43*, 3333−3336.

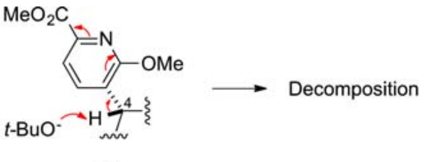
(13) A condensation reaction of **13** with nitromethane provided the double alkylated product **31**. In this nitro-aldol reaction, the generated hydroxyl group was readily captured by the *n*-butyl ester to give a five-membered lactone **29**. The subsequent *β*-elimination and conjugate addition of nitromethane afforded predominantly **31**. However, the bulky *tert*-butyl ester **14** did not undergo such a side reaction.



(14) The conditions of the four-step transformation of ester is as follows: (1) CSA, $HC(OMe)_3$, MeOH, reflux, 24 h, 70%; (2) KOH, H_2O, THF, 40 °C, 3 h; (3) *N,N′*-diisopropyl-*O*-*tert*-butylisourea, NH_4Cl, CH_2Cl_2, rt, 15 h; (4) 1 M HCl, THF, rt, 1.5 h, 80% (three steps). Direct formation of the *tert*-butyl ester **14** from **12** by a carbonylation reaction in the presence of *t*-BuOH did not proceed. In the carbonylation reaction of **12**, a higher temperature was necessary, probably because of the larger steric hindrance compared with **10**. Thus, *n*-butanol was used instead of methanol. The carbonylation reactions of **10** and **12** were promoted by either $Pd(OAc)_2$/DPPF or $Pd(dppf)Cl_2$.

(15) See Supporting Information for details.

(16) Undesired decomposition might be initiated by *t*-BuOK-mediated deprotonation at the C-4 position. In contrast, such deprotonation did not occur in the case of **27b**. Although we do not know the exact reason, steric repulsion between the *tert*-butyl ester and the pyrrolidine ring might prevent the proton at the C-4 position from taking a perpendicular position with respect to the pyridine ring, thereby decreasing its acidity.



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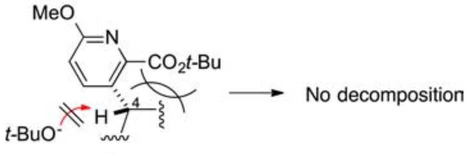

27b

(17) Selective removal of the *tert*-butyl ester of **21** was difficult due to the labile nature of the Dpm ester under acidic conditions. When the obtained diacid was subjected to the same epimerization conditions, an anhydride was formed intramolecularly and no epimerization occurred. Thus, ester **21** should be converted to the corresponding methyl ester **22**.

(18) Shibuya, M.; Tomizawa, M.; Suzuki, I.; Iwabuchi, Y. *J. Am. Chem. Soc.* **2006**, *128*, 8412−8413.