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Favorskii-Type Rearrangement of the 4,5-Epoxymorphinan Skeleton

Noriki Kutsumura,[†] Yasuaki Koyama,[‡] Yuko Suzuki,[‡] Ken-ichi Tominaga,[§] Naoshi Yamamoto,[†] Tsuyoshi Saitoh,[†] Yasuyuki Nagumo,[†] and Hiroshi Nagase*[,†,‡]

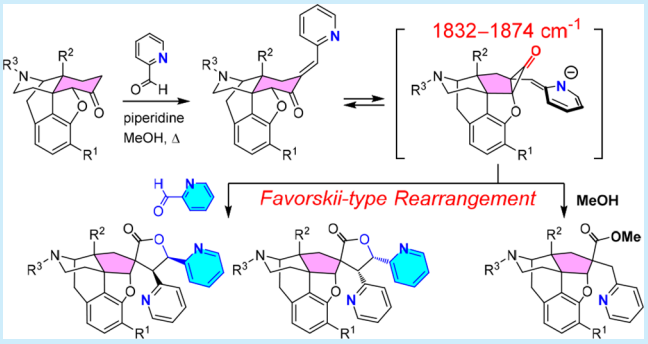
[†]International Institute for Integrative Sleep Medicine (WPI-IIIS), University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8575, Japan

[‡]Graduate School of Pure and Applied Sciences, University of Tsukuba, 1-1-1 Tennodai, Tsukuba, Ibaraki 305-8571, Japan

[§]National Institute of Advanced Industrial Science and Technology (AIST), Central 5 1-1-1 Higashi, Tsukuba, Ibaraki 305-8565, Japan

Supporting Information

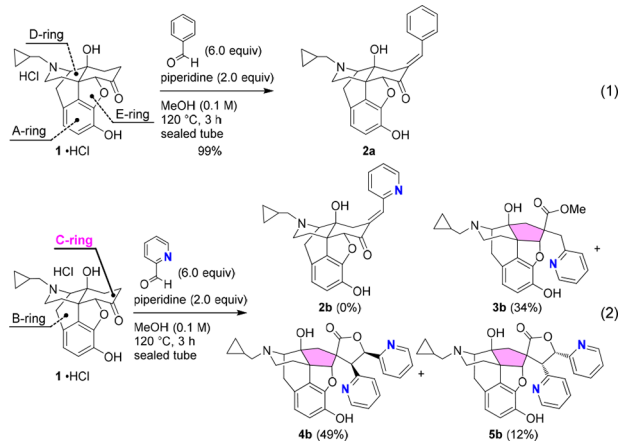
ABSTRACT: The aldol condensation of naltrexone with various aryl aldehydes gives the corresponding 7-benzylidenenaltrexone derivatives in high yields. However, novel C-ring-contracted morphinan compounds were produced when 2-pyridinecarboxaldehyde or its related analogues were used as a coupling partner. The key structural feature was the existence of the tetrahydrofuran ring (4,5-epoxy ring, E-ring) of the morphinan skeleton. The time-resolved in situ IR spectroscopy of the reaction system indicated the short-lived absorption of the distorted cyclopropanone intermediate.



Morphinan alkaloids, such as morphine and codeine, are pharmacologically important compounds and are widely known to express a variety of pharmacological actions (analgesia, addiction, antitussive, etc.) by acting on μ, δ, and κ opioid receptors (MOR, DOR, and KOR).[1] For the past quarter century, we have utilized a commercially available MOR antagonist, naltrexone (**1**), as a synthetic template to create many bioactive compounds.[2] For example, we recently reported that a DOR antagonist, 7-benzylidenenaltrexone (BNTX, **2a**) and its derivatives **2**, which were easily synthesized from **1**·hydrochloride (**1**·HCl), showed both chloroquine-resistance reversing activity for *Plasmodium chabaudi*[3] and antitrichomonal activity for *Trichomonas vaginalis*.[4] In these investigations, we discovered that the condensation of **1**·HCl with a 2-pyridinecarboxaldehyde unit led to an unprecedented Favorskii-type rearrangement reaction. Herein, we describe these results in detail.

Recently, we reported the efficient synthesis of the BNTX derivatives **2** by the aldol condensation of **1**·HCl with aryl aldehyde (Scheme 1, eq 1).[4a] On the other hand, the reaction of **1**·HCl with 2-pyridinecarboxaldehyde afforded the abnormal C-ring-contracted morphinan compounds **3b**, **4b**, and **5b** under the same conditions, although the desired compound **2b** was not detected (Scheme 1, eq 2). The structures of **4b** and **5b** were determined by 2D NMR (HSQC, HMBC, COSY, and NOESY), and the stereochemistry of **4b** was also confirmed from X-ray crystallography of **4b** (see Figure S1 and Table S2). Intriguingly, when 3- or 4-pyridinecarboxaldehydes were used as the coupling partner, this unprecedented reaction did not progress and afforded the corresponding compounds **2** in high

Scheme 1. Reaction of 1·HCl with Benzaldehyde (1) and Reaction of 1·HCl with 2-Pyridinecarboxaldehyde (2)



yields. The reaction of the salt-free **1** also gave the C-ring-contracted **3b**−**5b** (see Table S1). To the best our knowledge, there have been no reports regarding such C-ring contraction with the abnormal rearrangement on the morphinan skeletons. The commercially available **1**·HCl is one of the most useful synthetic templates to create bioactive morphinan alkaloids, and thus, we next examined a series of the reaction conditions to understand the details (Table 1).

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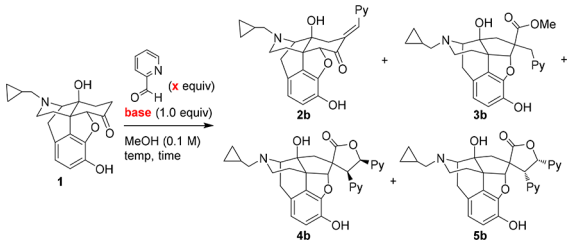
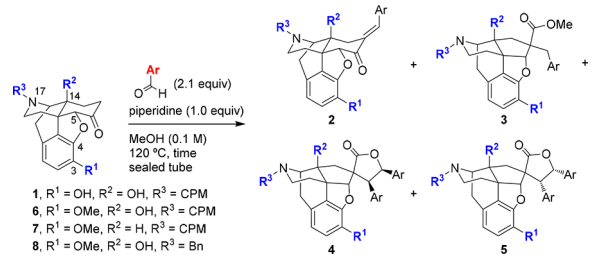
Table 1. Scope of the Reaction Conditions



entry	x (equiv)	base	temp (°C)	time	yields (%) 2b	3b	4b	5b
1	2.1	piperidine	120[a]	3 h		51	22	5
2	2.1	Et_3N	120[a]	2 d		29	28	4
3	2.1	DBU	120[a]	17 h		20	41	8
4	2.1	NaOMe	120[a]	3 h		18	41	9
5	1.1	piperidine	120[a]	8 h		86	8	
6	1.1	piperidine	rt	7 d		72	19	
7	10.0	piperidine	120[a]	3 h		18	57	15
8	10.0	piperidine[b]	120[a]	3 h	54	5	10	

[a]In sealed tube. [b]0.1 equiv of piperidine was used.

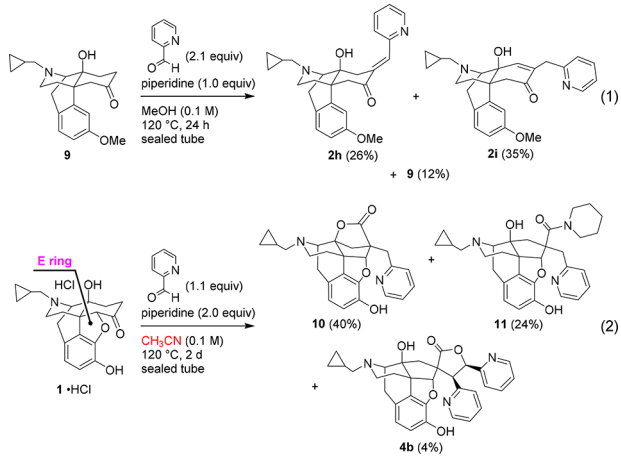
Table 2. Scope of the Reactant and Morphinan Substrates



entry		substrates R1	R2	R3	Ar	time (h)		yields (%) 2	3	4	5
1	**1**	OH	OH	CPM[a]		3	**c**	–	61	18	–
2	**1**	OH	OH	CPM[a]		4	**d**	–	43	33	5
3	**6**	OMe	OH	CPM[a]		3	**e**	–	10	68	13
4	**7**	OMe	H	CPM[a]		3	**f**	–	7	44	18
5	**8**	OMe	OH	Bn		3	**g**	–	18	63	13

[a]CPM = cyclopropylmethyl.

Scheme 2. Reaction of 9 without the E-Ring and Reaction of 1·HCl in CH_3CN



The C-ring contraction reaction of **1** proceeded by using not only piperidine, but also other bases, such as triethylamine, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), or sodium methoxide, though not with equal selectivity of the products (Table 1, entries 1−4). When 1.1 equiv of 2-pyridinecarboxaldehyde was used, the yield of the methyl ester **3b** was increased at any temperature (Table 1, entries 5 and 6). On the contrary, the spiro-γ-lactones **4b** and **5b** were preferentially generated when 10.0 equiv of the aldehyde was used (Table 1, entry 7). Interestingly, when 10.0 equiv of the aldehyde and catalytic amounts of piperidine were used, the BNTX derivative **2b** was first identified in 54% yield (Table 1, entry 8). The isolation of **2b** may have been caused by use of a larger excess of 2-pyridinecarboxaldehyde to trap piperidine, which is an essential base for the progress of the C-ring contraction reaction.

Next, we investigated the essential structural moieties in **1** and the aryl aldehyde for the reaction by using the condition of entry 1 in Table 1 (Table 2 and Scheme 2). As for the aryl aldehyde as a coupling partner, the 2-pyridinecarboxaldehyde moiety would be essential for the C-ring contraction (Table 2, entries 1 and 2, also see Table S1 for comparison). With respect to the 4,5-epoxymorphinan moiety, the 3-hydroxy group was not needed for the rearrangement because the 3-*O*-methylnaltrexone (**6**)[5] was converted to the respective products **3e**−**5e**, although the total ratio of the spiro-γ-lactones **4e** and **5e** was increased (Table 2, entry 3, vs Table 1, entry 1). In addition, the compound **7**[6] without a 14-hydroxy group and the compound **8** having a 17-*N*-benzyl group also afforded the C-ring-contracted **3f**−**5f** and **3g**−**5g**, respectively (Table 2, entries 4 and 5). On the other hand, it was noteworthy that the reaction of the morphinan **9**[7] lacking the tetrahydrofuran-ring (4,5-epoxy-ring, E-ring) with the aldehyde afforded the BNTX derivative **2h** (26%) and the structural isomer **2i** (35%) with slow reaction rates, and no C-ring-contracted compound was detected (Scheme 2, eq 1). This result suggested that the E-ring in the 4,5-epoxymorphinan structure could be essential for the C-ring contraction reaction. Moreover, the reaction of **1**·HCl with the aldehyde in acetonitrile was attempted because it seemed that the source of the methoxy group in the methyl ester of the compounds **3** would be the solvent (methanol). As a result, a bicyclo[2.2.1]lactone **10** was obtained as a major product together with a C-ring-contracted morphinan **11**, which was produced by the reaction of **10** with piperidine, and **4b** (Scheme 2, eq 2).

The proposed reaction mechanism for the formation of the C-ring-contracted morphinans **3**−**5** and **10** is illustrated in Scheme 3. The aldol condensation of **1** with 2-pyridinecarboxaldehyde in methanol produces the BNTX derivative **2b** as the first intermediate of this reaction. Then, **2b** is transformed to a cyclopropanone intermediate **B** through an enolate anion **A**, which is stabilized owing to the presence of the nitrogen of the pyridine moiety. The Favorskii-type rearrangement would take place in the presence of even a weak base because the neighboring oxygen atom of the E-ring and the ring strain of the C-ring[8] could enhance the acidity of the hydrogen at the C5 position (^{1}H NMR, 4.68 ppm). The reaction of **B** with another molecule of 2-pyridinecarboxaldehyde leads to the spiro-γ-lactones **4b** and/or **5b** through an intermediate **C**. In addition, a relatively stable cyclopropanone **D** generated by a

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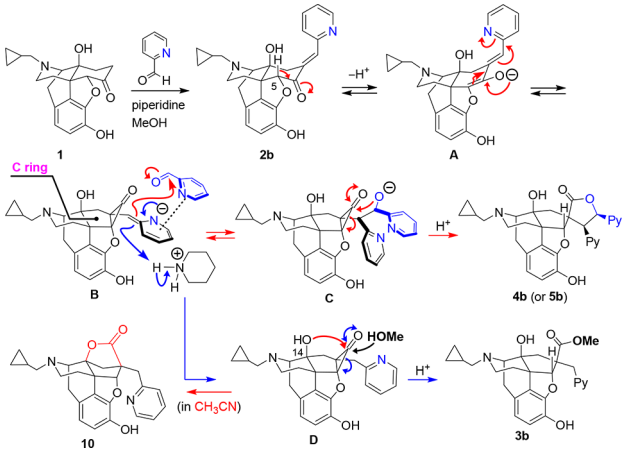
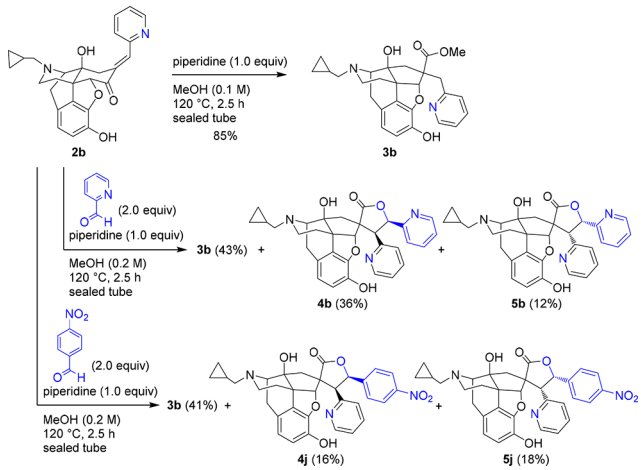
Scheme 3. Possible Mechanism for the Formation of 3b−5b and 10



protonation of **B** reacts with methanol to afford the methyl ester **3b**. When the reaction is carried out in acetonitrile, the intramolecular nucleophilic attack of the hydroxy group at the C14 position on the carbonyl group occurs to give the bicyclo[2.2.1]lactone **10**.

To confirm the proposed mechanism, we investigated the reactivity of the presumptive intermediate **2b**, which was synthesized under the conditions of entry 8 of Table 1 (Scheme 4). The reaction of **2b** with 1.0 equiv of piperidine in methanol

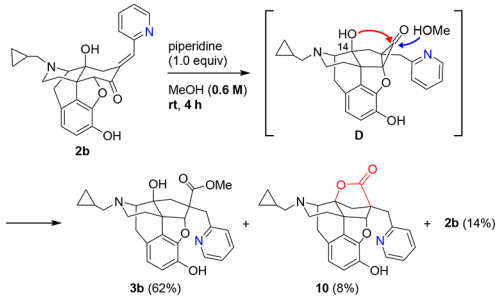
Scheme 4. Investigation of Reactivity of 2b



afforded only the methyl ester **3b** in high yield. Moreover, we also identified that the above reaction condition with 2-pyridinecarboxaldehyde afforded both the methyl ester **3b** and the spiro-γ-lactones **4b** and **5b**. Furthermore, as we expected, the reaction of **2b** with 4-nitrobenzaldehyde afforded the corresponding lactones **4j** and **5j** together with **3b**. These experimental results support the idea that the BNTX derivative **2b** was certainly the first reaction intermediate, while a variety of the spiro-γ-lactones derivatives **4** and **5** could be synthesized with ease by using this approach.

More supportive mechanistic information was also gained by using the time-resolved in situ IR spectroscopy (ReactIR) of the reaction progress. As shown in Scheme 5 and Figure 1, the methyl ester **3b** (1728 cm^{-1}) and the bicyclo[2.2.1]lactone **10** (1789 cm^{-1}) were produced when piperidine (1.0 equiv) was

Scheme 5. Reaction of 2b in MeOH (0.6 M) at Room Temperature



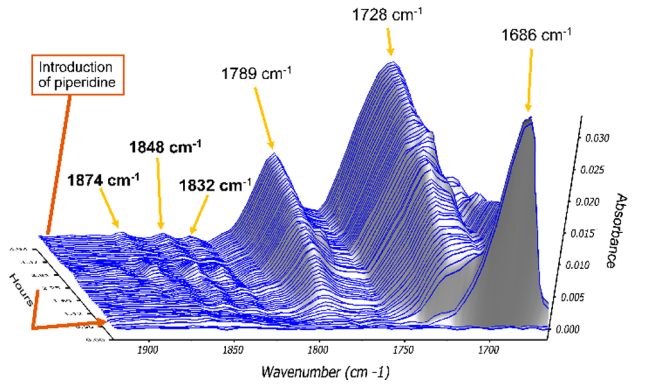


Figure 1. ReactIR spectra of the reaction of **2b** with piperidine in MeOH at room temperature.

added to a solution of **2b** (1686 cm^{-1}) in methanol (0.6 M) at room temperature.[9] Those IR absorption regions of **3b** and **10** were increased over time, whereas the α,β-unsaturated ketone stretch of **2b** was decreased. It should be noted that the distinguishing small peaks (1832, 1848, and 1874 cm^{-1}), which would correspond to the reported cyclopropanone absorption,[10] were always identified during the reaction (also see Figure S2). Additionally, we also carried out DFT calculations at the B3LYP/6-31+G* level of theory[11] for the hypothetical intermediate **D** to support the validity of the IR absorption of the cyclopropanone moiety on the 5-membered C-ring of these morphinan structures, such as **B**, **C**, or **D**, as shown in Scheme 3. As a result, the calculations indicated that the estimates of the carbonyl absorption of the intermediate **D** ranged from 1833 to 1856 cm^{-1}; that is, the theoretical IR values were close to the actual measured values (see Tables S3 and S4). These results support the idea that **2b** derived from **1** was transformed into the C-ring-contracted morphinans through the Favorskii-type rearrangement.

We also performed opioid receptor binding assays for novel morphinan derivatives **3b** and **4b** because the BNTX derivatives **2** have been previously reported to have the higher affinity for the δ opioid receptor (DOR) than the μ and κ opioid receptors (MOR and KOR).[4b,12] The resulting binding assay showed that the methyl ester **3b** possessed a relatively higher affinity for the KOR (MOR: K_i = 1.49 nM, DOR: K_i = 1.94 nM, KOR: K_i = 0.795 nM). On the other hand, the spiro-γ-lactone **4b** possessed quite a higher affinity for the DOR (MOR: K_i = 446 nM, DOR: K_i = 18.4 nM, KOR: K_i = 567 nM). These assays of the C-ring-contracted morphinans derived from the MOR antagonist **1** inspired us to obtain more potent and selective DOR and KOR ligands with the novel skeletons. We will report the details in the near future.

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In conclusion, we first discovered that the Favorskii-type rearrangement of 4,5-epoxymorphinan compounds occurred to produce the novel C-ring contracted morphinan skeletons by using 2-pyridinecarboxaldehyde or its related analogs. The reaction mechanism was supported by the isolation of the first intermediate **2b**, the experimental confirmation of the reactivity of **2b**, and the time-resolved in situ IR spectroscopy of the reaction system.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.8b00288.

Experimental procedures, characterization data, ^{1}H and ^{13}C NMR spectra of all new compounds, and DFT calculations (PDF)

Accession Codes

CCDC 1817651 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: nagase.hiroshi.gt@u.tsukuba.ac.jp.

ORCID

Noriki Kutsumura: 0000-0002-1494-2133
Ken-ichi Tominaga: 0000-0002-6078-2169
Hiroshi Nagase: 0000-0003-0428-3979

Notes

The authors declare no competing financial interest.

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(9) The ReactIR analysis (Figure 1) and the confirmatory experiment (Scheme 5) were carried out in high concentration (0.6 M) at room temperature; hence, the bicyclo[2.2.1]lactone **10** was also produced, unlike in the case of Scheme 4.

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