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A Double Decarboxylation Reaction of an Oxazolidinone and Carboxylic Acid: Its Application to the Synthesis of a New Opioid Lead Compound

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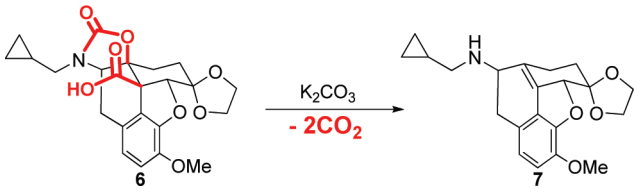
Received December 4, 2009



Treatment of oxazolidinone carboxylic acid **6** with potassium carbonate gave olefin **7** by a double decarboxylation reaction. The reaction was proposed to proceed via decarboxylation followed by E1cB-like mechanism. 15,16-Nornaltrexone derivative **17** prepared from double decarboxylation product **7** showed strong affinity for the μ opioid receptor, indicating it to be a new opioid lead compound.

Three types of opioid receptors (μ, δ, κ) are now well-established not only by pharmacological studies but also by molecular biological studies.[1] The μ receptor type is believed to be linked to narcotic addiction, and therefore, δ and κ types are promising drug targets for analgesics without addiction. A putative ε receptor, which has not yet been cloned, has also been proposed as another opioid receptor type, and extensive pharmacological data support its existence.[2] To obtain ideal analgesics without addiction and without other side effects derived from the μ receptor, we have synthesized various kinds of naltrexone derivatives and have reported selective agonists for δ, κ, and putative ε receptor.[3−5] Moreover, we have also reported many new reactions using naltrexone derivatives.[6] Recently, we reported the 16−17 bond cleavage reaction of the naltrexone derivative **1** to afford oxazolidinone derivative **2** (Scheme 1).[6f] This cleavage reaction is the first D ring-opening reaction in the 4,5-epoxymorphinan skeleton and prompted us to reinvestigate an opioid receptor−ligand binding model, the Beckett−Casy model,[7] using 4,5-epoxymorphinan derivatives cleaved in their D rings.[8] In the course of the investigation, we found a novel double decarboxylation reaction, and one of the resulting derivatives showed stronger affinity for the μ receptor than did the classical and clinically used μ agonist morphine. Herein, we describe a novel double decarboxylation reaction and its application to synthesis of opioid derivatives with a novel skeleton.

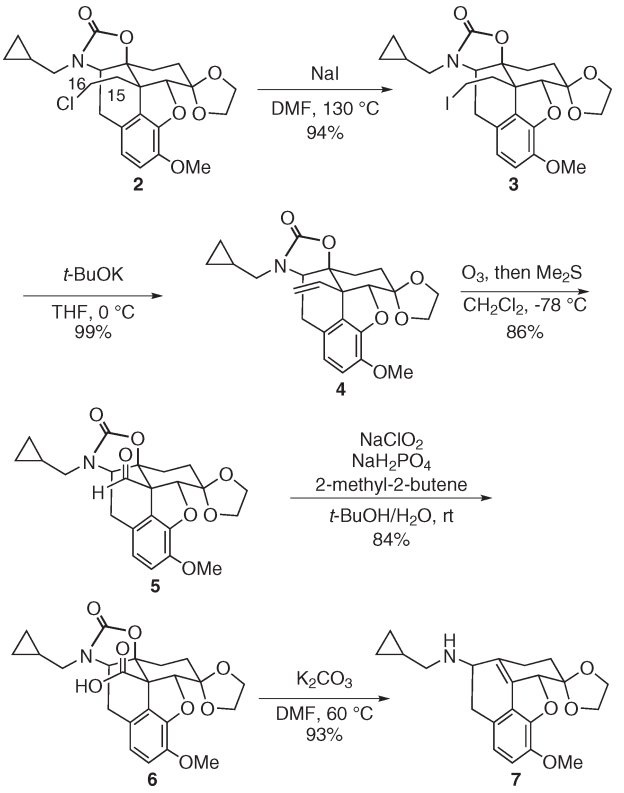
SCHEME 1. C16−N17 Cleavage Reaction

Naltrexone acetal **1** was treated with 1-chloroethyl chloroformate (ACE-Cl) in the presence of potassium carbonate in 1,1,2,2-tetrachloroethane (TCE) to give oxazolidinone chloride **2** (Scheme 1),[6f] followed by treatment with sodium iodide to afford iodide **3** in 94%. Ozonolysis of compound **4**,

(1) Dhawan, B. N.; Cesselin, F.; Reisine, T.; Bradley, P. B.; Portoghese, P. S.; Hamon, M. *Pharmacol. Rev.* **1996**, *48*, 567.
(2) Fujii, H.; Nagase, H. *Curr. Med. Chem.* **2006**, *13*, 1109 and references therein.
(3) κ agonists: (a) Kawai, K.; Hayakawa, J.; Miyamoto, T.; Imamura, Y.; Yamane, S.; Wakita, H.; Fujii, H.; Kawamura, K.; Matsuura, H.; Izumimoto, N.; Kobayashi, R.; Endo, T.; Nagase, H. *Bioorg. Med. Chem.* **2008**, *16*, 9188. (b) Nemoto, T.; Fujii, H.; Narita, M.; Miyoshi, K.; Nakamura, A.; Suzuki, T.; Nagase, H. *Bioorg. Med. Chem. Lett.* **2008**, *18*, 6398. (c) Nagase, H.; Watanabe, A.; Nemoto, T.; Yamaotsu, N.; Hayashida, K.; Nakajima, M.; Hasebe, K.; Nakao, K.; Mochizuki, H.; Hirono, S.; Fujii, H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 121.
(4) δ agonists: (a) Nagase, H.; Kawai, K.; Hayakawa, J.; Wakita, H.; Mizusuna, A.; Matsuura, H.; Tajima, C.; Takezawa, Y.; Endoh, T. *Chem. Pharm. Bull.* **1998**, *46*, 1695. (b) Nagase, H.; Yajima, Y.; Fujii, H.; Kawamura, K.; Narita, M.; Kamei, J.; Suzuki, T. *Life Sci.* **2001**, *68*, 2227. (c) Nagase, H.; Osa, Y.; Nemoto, T.; Fujii, H.; Imai, M.; Nakamura, T.; Kanemasa, T.; Kato, A.; Gouda, H.; Hirono, S. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 2792.
(5) A putative ε agonist: Fujii, H.; Narita, M.; Mizoguchi, H.; Murachi, M.; Tanaka, T.; Kawai, K.; Tseng, L. F.; Nagase, H. *Bioorg. Med. Chem.* **2004**, *12*, 4133.
(6) (a) Fujii, H.; Hirano, N.; Uchiro, H.; Kawamura, K.; Nagase, H. *Chem. Pharm. Bull.* **2004**, *52*, 747. (b) Watanabe, A.; Kai, T.; Nagase, H. *Org. Lett.* **2006**, *8*, 523. (c) Osa, Y.; Ida, Y.; Furuhata, K.; Nagase, H. *Heterocycles* **2006**, *69*, 271. (d) Nagase, H.; Watanabe, A.; Nemoto, T.; Yamamoto, N.; Osa, Y.; Sato, N.; Yoza, K.; Kai, T. *Tetrahedron Lett.* **2007**, *48*, 2547. (e) Nemoto, T.; Fujii, H.; Sato, N.; Nagase, H. *Tetrahedron Lett.* **2007**, *48*, 7413. (f) Fujii, H.; Imaide, S.; Watanabe, A.; Nemoto, T.; Nagase, H. *Tetrahedron Lett.* **2008**, *49*, 6293. (g) Nagase, H.; Watanabe, A.; Harada, M.; Nakajima, M.; Hasebe, K.; Mochizuki, H.; Yoza, K.; Fujii, H. *Org. Lett.* **2009**, *11*, 539. (h) Fujii, H.; Ogawa, R.; Ohata, K.; Nemoto, T.; Nakajima, M.; Hasebe, K.; Mochizuki, H.; Nagase, H. *Bioorg. Med. Chem.* **2009**, *17*, 5983. (i) Fujii, H.; Watanabe, A.; Nemoto, T.; Narita, M.; Miyoshi, K.; Nakamura, A.; Suzuki, T.; Nagase, H. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 438.
(7) (a) Beckett, A. H.; Casy, A. F. *J. Pharm. Pharmacol.* **1956**, *6*, 986. (b) Beckett, A. H. *J. Pharm. Pharmacol.* **1956**, *8*, 848. (c) Casy, A. F.; Parfitt, R. T. In *Opioid Analgesics, Chemistry and Receptors*; Plenum Press: New York, 1986; pp 473−475.
(8) Imaide, S.; Fujii, H.; Watanabe, A.; Nemoto, T.; Nakajima, M.; Nakao, K.; Mochizuki, H.; Nagase, H. *Bioorg. Med. Chem. Lett.* DOI 10.1016/j.bmcl.2009.12.039.

DOI: 10.1021/jo9025463 Published on Web 01/13/2010

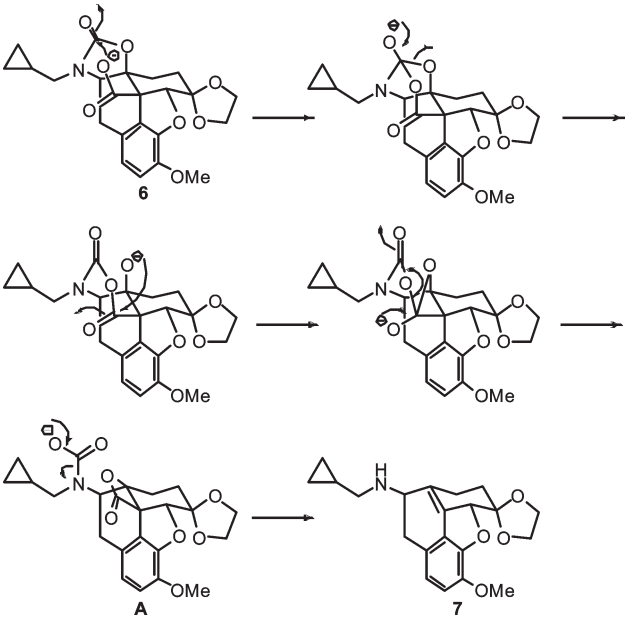
SCHEME 2. Elimination of the C15, C16 Moiety



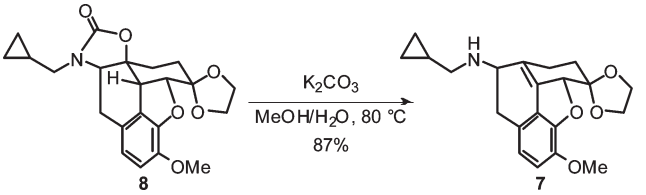
prepared from iodide **3** by an elimination reaction, gave aldehyde **5**. The resulting aldehyde **5** was oxidized with sodium chlorite (Pinnick oxidation)[9] to afford carboxylic acid **6**. When the acid **6** was treated with potassium carbonate in DMF, surprisingly, two carbon dioxide units (carboxyl group and oxazolidinone unit) were simultaneously eliminated to give olefin **7** in 93% yield (Scheme 2). The structure of compound **7** was determined by X-ray crystallography.

The mechanism of the double decarboxylation reaction of **6** was assumed to proceed via four-membered ring intermediate (β-lactone) **A** (Scheme 3).[10−12] However, the treatment of compound **8**, which lacks a carboxyl group, with potassium carbonate in methanol and water also afforded the same decarboxylated compound **7** in 87% yield (Scheme 4), while the same treatment in DMF furnished the

SCHEME 3. Proposed Decarboxylation Mechanism of 6 via Four-Membered Ring Intermediate A



SCHEME 4. Decarboxylation of Oxazolidinone 8



recovery of compound **8**. This result may suggest an E2 or E1cB elimination mechanism[13,14] rather than a mechanism that proceeds via a β-lactone. Although the E2 elimination usually proceeds via an antiperiplanar transition state, the C−O bond of the oxazolidinone ring and the carboxyl group in **6**, and the hydrogen in **8**, respectively, lie in a synclinal conformation, suggesting that the elimination reaction would not likely occur via an E2 fashion.[15,16] Therefore, the double decarboxylation reaction would proceed by E1cB mechanism, in which a carbanion **B**, arising from the first decarboxylation of compound **6** or the deprotonation in compound **8** by potassium carbonate, might be stabilized by the phenyl ring and/or the carbonyl group in the oxazolidinone ring (Figure 1).

The decarboxylation of oxazolidinones **6** and **8** is seemingly similar to removal of the well-known amino protective group, the Fmoc group. Fmoc deprotection occurs

(9) Bal, B. S.; Childers, W. E. Jr.; Pinnick, H. W. *Tetrahedron* **1981**, *37*, 2091.

(10) Hara, S.; Taguchi, H.; Yamamoto, H.; Nozaki, H. *Tetrahedron Lett.* **1975**, *16*, 1545.

(11) The thermal decarboxylation of a β-lactone has been widely used for preparation of an olefin. (a) Pommier, A.; Pons, J.-M. *Synthesis* **1993**, 441. (b) Rayner, C. M. In *Comprehensive Organic Functional Group Transformations*; Katritzky, A. R., Meth-Cohn, O., Rees, C. W., Eds.; Pergamon Press: Oxford, 1995; Vol. 1, pp 673−718.

(12) Recent examples of the thermal decarboxylation of β-lactones: (a) Braun, N. A.; Meier, M.; Schmaus, G.; Hölscher, B.; Pickenhagen, W. *Helv. Chim. Acta* **2003**, *86*, 2698. (b) Merlic, C. A.; Doroh, B. C. *J. Org. Chem.* **2003**, *68*, 6056. (c) Buckle, M. J. C.; Fleming, I.; Gil, S.; Pang, K. L. C. *Org. Biomol. Chem.* **2004**, *2*, 749. (d) Shindo, M.; Matsumoto, K.; Shishido, K. *Chem. Commun.* **2005**, 2477. (e) Shindo, M.; Matsumoto, K.; Shishido, K. *Tetrahedron* **2007**, *63*, 4271.

(13) Olefins have been prepared by elimination reaction in which oxazolidinone functioned as a leaving group. (a) Danishefsky, S. J.; Panek, J. S. *J. Am. Chem. Soc.* **1987**, *109*, 917. (b) Gates, K. S.; Silverman, R. B. *J. Am. Chem. Soc.* **1989**, *111*, 8891. (c) Padwa, A.; Brodney, M. A.; Lynch, S. M.; Rashatasakhon, P.; Wang, Q.; Zhang, H. *J. Org. Chem.* **2004**, *69*, 3735.

(14) Another possible mechanism is discussed in the Supporting Information.

(15) Some examples of syn elimination have been reported in molecules in which β-hydrogen and leaving group could not achieve an antiperiplanar conformation. Smith, M. B.; March, J. In *March's Advanced Organic Chemistry*; 6th ed.; John Wiley & Sons: New York, 2007; pp 1482−1483 and references therein.

(16) In cyclic systems, the extent of anti and syn elimination depends on ring size. Cyclohexyl systems have a very strong preference for anti elimination. (a) Carey, F. A.; Sundberg, R. J. In *Advanced Organic Chemistry, Part A: Structure and Mechanisms*; 5th ed.; Springer: New York, 2007; p 559. (b) See also ref 15.

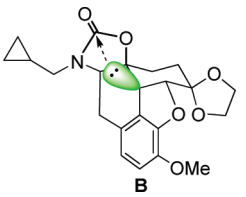
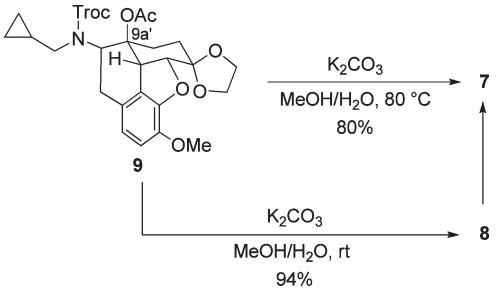
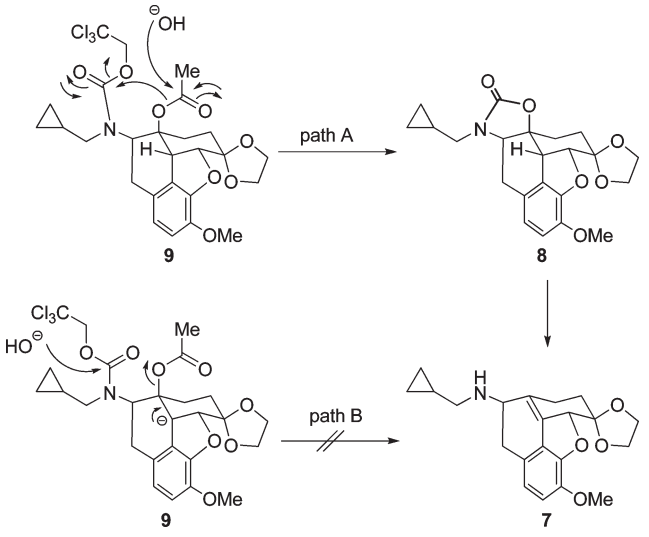


FIGURE 1. Possible effect of the carbonyl group in the oxazolidinone ring on stabilizing carbanion **B**.

SCHEME 5. Elimination Reaction of Compound 9



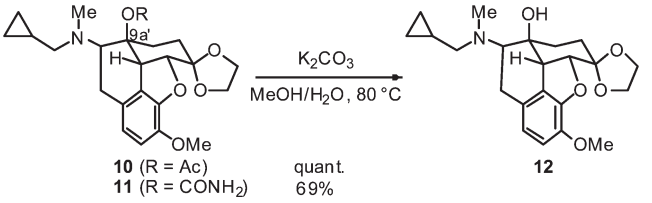
SCHEME 6. Proposed Decarboxylation Mechanism of 9 via Oxazolidinone 8



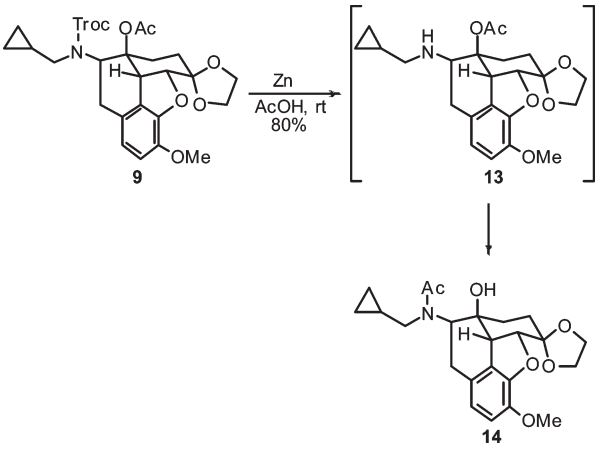
through cleavage by a weak base such as an amine via elimination and simultaneous decarboxylation.[17]

Compound **7** was also obtained by the treatment of 9a′-acetyl-*N*-trichloroethoxycarbonyl derivative **9** with potassium carbonate in methanol and water at 80 °C in 80% yield (Scheme 5). Compound **7** was proposed to be produced by decarboxylation of **8** (Scheme 6, path A) because the treatment of compound **9** with potassium carbonate at room temperature gave oxazolidinone **8** (Scheme 5), which was converted into compound **7** by the same treatment at 80 °C (Scheme 4). Another possible route was via respective hydrolysis of carbamate and elimination of acetate (Scheme 6, path B). However, path B can be ruled out by the following results. First, hydrolysis of the carbamate required harsher reaction conditions and longer reaction time.[6f] Second, 9a′-acetate **10** was hydrolyzed under basic conditions to give only compound **12** (Scheme 7). Finally, treatment of compound **9** with zinc in acetic acid afforded acetamide **14** by migration of the acetyl group (Scheme 8), which was never converted into olefin **7** with basic treatment. Taken together, these results strongly suggest that compound **7** would be obtained via oxazolidinone **8** (path A) but not by path B (Scheme 6), indicating that the oxazolidinone structure may play an important role in the second decarboxylation reaction. Moreover, treatment of acyclic carbamate **11** with potassium carbonate gave only compound **12** by hydrolysis. This result supports the importance of the cyclic carbamate, oxazolidinone structure in the second decarboxylation reaction.

SCHEME 7. Hydrolysis of 9a′-Acetate 10 and 9a′-Carbamate 11



SCHEME 8. Removal of the Troc Protective Group and Migration of the Acetyl Group

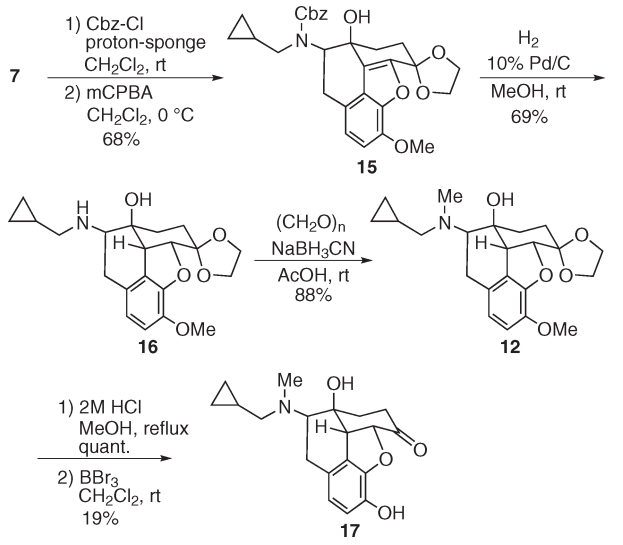


Compound **7** has a novel structure that loses the D ring (see Scheme 1) from its 4,5-epoxymorphinan skeleton. Therefore, we next evaluated the affinity of compound **17**, derived from **7**, for the opioid receptor. Compound **17** was prepared from **7**, as shown in Scheme 9. The secondary amino group in olefin **7** was protected by a Cbz group followed by oxidation with mCPBA and subsequent hydrogenation of **15** to provide compound **16**. The stereochemistries of compounds **15** and **16** were determined by 2D NMR experiments of their analogues.[18] Compound **16** was converted into compound **12** by reductive alkylation, followed by acidic deprotection of the acetal and subsequent demethylation with BBr_3 to give the objective compound **17**. In the competitive binding assay,[6h] compound **17** showed stronger binding affinity (K_i = 1.17 nM) for the μ receptor than that of morphine (K_i = 1.98 nM), thus indicating that it could be a new lead compound useful for designing receptor-type-selective opioid ligands.

(17) Clayden, J.; Greeves, N.; Warren, S.; Wother, P. In *Organic Chemistry*; Oxford University Press: New York, 2001; pp 496−497.

(18) Determination of the stereochemistries of compounds **15** and **16** is described in the Supporting Information.

SCHEME 9. Synthesis of 15,16-Nornaltrexone Derivative 17



In conclusion, base treatment of oxazolidinone carboxylic acid **6** led to the double decarboxylation reaction, affording olefin **7**. We examined the reaction mechanism and proposed an E1cB-like mechanism via carbanion **B** but not via a β-lactone intermediate. The double decarboxylation product **7** was converted into compound **17**, which showed stronger affinity for the μ receptor than morphine.

Experimental Section

Double Decarboxylation Reaction of Compound 6. Under argon, to a solution of compound **6** (4.3 g, 9.7 mmol) in DMF (80 mL) was added potassium carbonate (2.9 g, 21.3 mmol) with stirring at 60 °C for 15 h. The reaction mixture was poured into distillated water and extracted with chloroform, and then dried over anhydrous sodium sulfate. After removing the solvent under reduced pressure, the residue was purified by crystallization from ethyl acetate solution to give compound **7** (3.2 g, 93%) as white needles.

Decarboxylation Reaction of Compound 8. Under argon, to a solution of compound **8** (11 mg, 0.028 mmol) in methanol (1 mL) was added saturated potassium carbonate solution (1 mL), and the mixture was stirred at 80 °C for 19 h. The reaction mixture was poured into distillated water and extracted with chloroform, and then dried over anhydrous sodium sulfate. After removing the solvent under reduced pressure, the residue was purified by silica gel column chromatography ($CHCl_3$/MeOH = 100/0 to 100/3) to give compound **7** (8.5 mg, 87%) as white needles.

(3a′*R*,9′*R*,*E*)-*N*-(Cyclopropylmethyl)-5′-methoxy-1′,3a′,8′,9′-tetrahydro-2′*H*-spiro[1,3-dioxolane-2,3′-phenanthro[4,5-*bcd*]-furan]-9′-amine (7): mp 122−123 °C; ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.06−0.24 (m, 2H), 0.42−0.60 (m, 2H), 0.90−1.06 (m, 1H), 1.89 (dd, J = 6.0, 14.1 Hz, 1H), 1.96−2.10 (m, 1H), 2.18−2.34 (m, 1H), 2.47−2.70 (m, 3H), 2.79 (dd, J = 13.2, 14.7 Hz, 1H), 2.93 (dd, J = 6.9, 15.0 Hz, 1H), 3.61−3.73 (m, 1H), 3.86−4.12 (m, 3H), 3.87 (s, 3H), 4.28 (dt, J = 5.1, 6.3 Hz, 1H), 5.26 (q, J = 3.6 Hz, 1H), 6.58 (d, J = 8.1 Hz, 1H), 6.62 (d, J = 7.8 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 3.3, 3.4, 11.7, 26.0, 30.7, 33.1, 51.7, 56.8, 60.7, 65.3, 66.3, 85.6, 107.0, 113.6, 119.7, 123.7, 127.3, 129.1, 133.1, 143.0, 145.5; IR (KBr, cm^{-1}) 3449, 2882, 1509, 1160, 1104, 951; HR−MS (DART) $[M + H]^+$ calcd for $C_{21}H_{26}NO_4$ 356.1856, found 356.1865.

Acknowledgment. We acknowledge the financial support from a Grant-in-Aid for Scientific Research (C) (19590105), Shorai Foundation for Science, and the Uehara Memorial Foundation. We also acknowledge the Institute of Instrumental Analysis of Kitasato University, School of Pharmacy for its facilities.

Supporting Information Available: Experimental procedures, characterization data for new compounds, discussion of another possible mechanism, determination of the stereochemistries of compounds **15** and **16**, X-ray data for **7**, and copies of NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.