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Convenient Synthesis of Oxazolidinones by the Use of Halomethyloxirane, Primary Amine, and Carbonate Salt

Yumiko Osa, Yuka Hikima, Yoko Sato, Kouichi Takino, Yoshihiro Ida, Shuichi Hirono, and Hiroshi Nagase*

School of Pharmaceutical Sciences, Kitasato University, 5-9-1, Shirokane, Minato-ku, Tokyo 108-8641, Japan

nagaseh@pharm.kitasato-u.ac.jp

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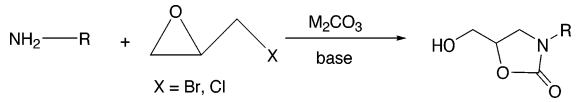
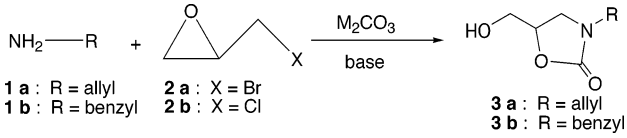


Primary amines reacted with carbonate salts (Na_2CO_3, K_2CO_3, Cs_2CO_3, and Ag_2CO_3) and halomethyloxiranes in the presence of a base such as DBU or TEA to give oxazolidinones in high yields. The use of K_2CO_3 among these carbonate gave the best yield in this synthesis. A reaction mechanism was proposed that the oxazolidinone was obtained from an oxazinanone intermediate via a bicyclo[2.2.1] intermediate. The present reaction can be widely applied to convenient synthesis of useful N-substituted oxazolidinones and chiral oxazolidinones.

Oxazolidinones can be used as the precursors of naturally occurring amino alcohols and amino acids which have been synthesized by a variety of methods.[1] In addition, they are useful as chiral auxiliaries[2] in asymmetric synthesis.[1a] Recently, some oxazolidinone derivatives such as DUP-105,[3] DUP-721,[3] and linezolid (Zyvox)[3b,4] have attracted much interest as monodrug- or multidrug-resistant antibacterial agents.[5] Early synthesis of oxazolidinones was carried out via the reactions of 1,2-amino alcohols and phosgene or its derivatives[6] or amino alcohols with carbon dioxide under high pressure.[7] Recently, carbohydrate derivatives were also used in the synthesis of oxazinanone and oxazolidinone.[8] However, these methods required multiple steps, and the total yields were not always high. As an improved method to overcome the defects, cyclic carbamate synthesis by use of carbon dioxide dissolved in protic solvents containing amines and oxiranes was reported by Toda et al.[9] When primary amines reacted with halomethyloxiranes and a large amount of carbon dioxide under neutral conditions, six-membered cyclic carbamates of oxazinanones were formed.[10] They proposed a reaction mechanism by which the ammonium carbamate intermediate reacted with oxirane. They also used 2-(1-haloalkyl)oxirane and primary amine in the presence of cesium carbonate (Cs_2CO_3) and proposed a mechanism by which carbon dioxide derived from Cs_2CO_3 reacted with the intermediate (2-alkyl-3-aminomethyloxirane) to form oxazolidinone.[11] However, these reactions did not give a high yield of oxazolidinone.

SCHEME 1



We have recently found a simple method to synthesize oxazolidinone derivatives using primary amine and halomethyloxirane in the presence of various carbonate salts. The reaction is shown in Scheme 1.

At the beginning of our research, we used allylamine (**1a**, 2 molar equiv), which reacted with halomethyloxirane (**2**, 2 molar equiv, bromomethyloxirane **2a,** and chloromethyloxirane **2b**) in the presence of potassium carbonate or silver carbonate (1 molar equiv) in methanol at room temperature to afford oxazolidinone in 45% yield. The structure of *N*-allyl-5-hydroxymethyloxazolidin-2-one

* To whom correspondence should be addressed. Tel: +81-3-5791-6372. Fax: +81-3-4442-5707.

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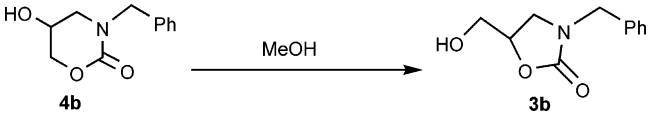
TABLE 1. Conversion Conditions of Six-Membered Ring 4b to Five-Membered Ring 3b



4b 3b

	molar ratio			yield (%)	
run[a]	**4b**/**1b**[b]/ K_2CO_3/base	base (equiv)	reaction	**3b**	recovery **4b**
1	1:0:0:0		reflux, o.n.[c]		100
2	2:2:1:0		rt, stirring, o.n.	94	
3	2:2:1:0		reflux, 2 hr	quant	
4	1:0:0:5	DBU	reflux, 5.5 hr	96	
5	1:0:0:5	TEA	reflux, o.n.		100
6	1:0:0:4	TEA (3), DBU (1)	reflux, o.n.	quant.	

[a] All reactions were carried out in MeOH. [b] **1b** = NH_2CH_2-Ph. [c] o.n. = overnight.

(**3a**) obtained from allylamine (**1a**) was determined, in detail, using ^{1}H NMR, ^{13}C NMR, ^{1}H−^{1}H decoupling, NOE, and LSPD[12] and also was supported by X-ray analysis.[13] Furthermore, it was confirmed that the carbon of the carbonate salt was introduced at the 2-position in **3a** by the reaction using isotopic $Ag_2{}^{13}CO_3$ (98% atomic purity of ^{13}C) instead of K_2CO_3.

To elucidate the reaction mechanism and increase the yields, the IR spectrum of the reaction mixture, which was obtained by the reaction of molar ratios of K_2CO_3 (1 mol), benzylamine (instead of allylamine because of its high boiling point compared with that of allylamine), and bromomethyloxirane (2 mol) in methanol at 0 °C, was measured. We found the bands at 1680 and 1730 cm^{-1} in the reaction mixture. The former band is assigned[14] to a six-membered cyclic carbamate of oxazinanone, which was also reported by Toda et al.[9e] The latter band corresponds to a five-membered cyclic carbamate of oxazolidinone. The spot of oxazinanone in TLC (the value of R_f was 0.47; chloroform/methanol = 10:1) diminished with the reaction time. On the other hand, the spot of oxazolidinone in TLC (the value of R_f was 0.58; chloroform/methanol = 10:1) enlarged with the reaction time. These facts support that oxazinanone is an unstable intermediate (kinetic product) in the reaction.

For further confirmation of oxazinanone formation in the reaction process, the isomerization of *N*-benzyl-5-hydroxyoxazinanone (**4b**) to *N*-benzyl-5-hydroxymethyloxazolidinone (**3b**) was examined as shown in Table 1. When only **4b** was refluxed in methanol, **3b** was not obtained and **4b** was recovered (run 1). On the other hand, the reaction conditions (even if at room temperature) for oxazolidinone synthesis in the presence of K_2CO_3 gave **3b** in 94% yield (run 2). These facts showed that K_2CO_3 is necessary for the conversion of **4b** to **3b**. Furthermore, under reflux for 2 h, **3b** was obtained quantitatively (run 3). The use of DBU instead of K_2CO_3 also gave **3b** in 96% yield (run 4), but by the use of TEA instead of K_2CO_3 **4b** was quantitatively recovered (run 5). When 1 equiv of DBU was added after addition of 3 equiv of TEA to the reaction solution, **3b** was obtained in quantitative yield (run 6). The above results showed that the ring contraction reaction from six-membered cyclic carbamate to five-membered cyclic carbamate perfectly proceeded in the presence of K_2CO_3 or DBU but did not occur in the presence of only TEA. These results mean that a strong base or a basic condition is necessary to form **3b**.

Furthermore, total molecular energy calculation of compounds **3b** and **4b** was carried out by the use of Merck Molecular Force Field (MMFF94).[15] The total energy of **3b** is 31.2 kcal/mol and that of **4b** is 34.1 kcal/mol. Therefore, the calculation result shows that oxazolidinone is more stable than oxazinanone. This result also supports that the six-membered ring is an intermediate of the reaction process. Wang et al. also reported six-membered ring oxazinanone was converted to more stable 5-membered ring oxazolidinone under base conditions and heating,[8i] which gave supporting evidence in our present conversion.

Based on the above discussion, a reaction mechanism is proposed as depicted in Scheme 2. Two routes (I and II) are supposed to form an intermediate D. In route I, first, primary amine **1** attacks the C−X bond of halomethyloxirane **2** to afford an intermediate A. Subsequently, a carbonate ion attacks A to form the intermediate D. In route II, **1** attaches the oxirane ring of **2** to give intermediate B. As oxirane ring **2** may be more electrophilic than the C−X bond in the case of an attack of the alkoxide ion,[16] a first attack of amine **1** to the oxirane ring may be reasonably considered.[16,17] Subsequently, the resulting alkoxide ion of intermediate B attacks the carbon atom of the halomethyl group to form C. Next, the carbonate ion attacks the oxirane ring C to afford the intermediate D. Then the resulting amino nitrogen attacks the carbonyl group in D to cyclize intramolecularly to a six-membered ring of oxazinanone (**4**). In the mechanism, the intermediate D can cyclize only to six-membered oxazinanone, not five-membered oxazolidinone. Two routes III and IV are considered as the conversion process of oxazolidinone (**3**) from compound **4**. In route III, the alkoxide ion in intermediate E under strong basic condition attacks intramolecularly the carbonyl carbon to give a bicyclo[2.2.1] intermediate F, which is subsequently converted to a five-membered ring of oxazolidinone **3**. In route IV, a methoxide ion generated from methanol under strong basic condition attacks the carbonyl carbon of the oxazinanone (intermediate G) to open a ring structure. The resulting alkoxide ion (intramolecularly) attacks the carbon of intermediate H to form compound **3**. However, it is considered that the intramolecular attack in route III may be more favorable (entropy) than the intermolecular one of the methoxide

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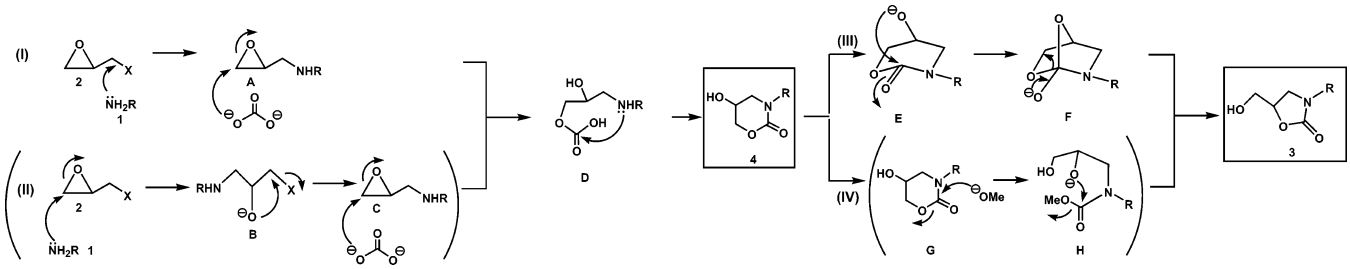
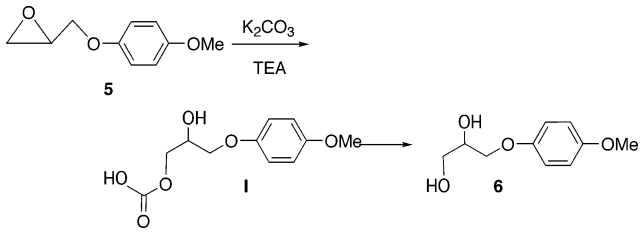
(17) The textbook of organic chemistry (for example, the book written by Warren[16]) described the oxirane ring of epichlorohydrin is more electrophilic than the C−Cl bond with alkoxide. Therefore, the carbonate ion was reacted with the oxirane ring of epibromohydrin.

SCHEME 2



SCHEME 3



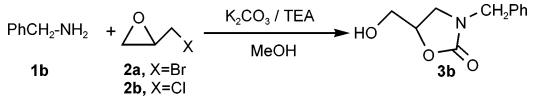
ion in route IV. Therefore, we think route III may be more reasonable. Compound **4** will be formed as a kinetic product and **3** can be obtained as a thermodynamic product.

The difference between our mechanism and that of Toda was mainly the reaction intermediate. In the Toda mechanism,[11] the carbamate anion was formed by reacting 2-(1-haloalkyl)oxirane and amine with CO_2 derived from Cs_2CO_3 to open the epoxide in the alkaline medium and the resulting alkoxide ion attacks at the C−X carbon to give an epoxy ring. However, as carbonate (Cs_2CO_3) could not be converted to CO_2 under the strong basic condition using CsOH, CO_2 could not be produced to form the carbamate ion. In our mechanism, the carbonate ion, not the carbamate anion, attacks the halomethyloxirane directly.

Furthermore, the reactivity (nucleophilicity) of the carbonate ion was confirmed by the reaction of 2,3-epoxypropyl 4-methoxyphenyl ether (**5**) and K_2CO_3. Though the reaction of **5** and K_2CO_3 (dried in vacuo at 120 °C for 10 h) in anhydrous DMF gave no products under the anhydrous condition, the addition of TEA to the solution containing **5** and K_2CO_3 in anhydrous DMF under anhydrous condition afforded a diol (**6**) which was obtained by hydrolysis of the carbonate intermediate I in 43% yield[18] (Scheme 3). The preparation of the product, diol (**6**), suggests attack of the carbonate ion to oxirane in the presence of a base.

On the basis of the above proposed reaction mechanism as shown in Scheme 2, we examined optimization of the reaction conditions. In Scheme 2, the excess of reagents for primary amine was expected to increase the yields, and strong basic condition would be needed for formation for the alkoxide ion to attack the carbonyl carbon (E, F) and reflux condition would be able to convert the six-membered ring, oxazinanone, to the five-membered ring, oxazolidinone, easily. Table 2 shows various conditions to optimize various molar ratios of the reagents and temperature. The high yield of *N*-benzyl-5-hydroxymethyloxazolidin-2-one (**3b**) (more than 80% yield) was obtained under the conditions of a large mole ratio (more than 5 molar equiv) of halomethyloxirane, K_2CO_3 in methanol in the presence of more than 5 mol base (TEA; triethylamine or DBU; 1,8-diazabicyclo[5.4.0]undec-7-ene) per mole of amine under reflux (runs 7, 9, and 10).

TABLE 2. Reaction Conditions for Synthesis of 3b



run	X	molar ratio **1b**/**2**/K_2CO_3/TEA	reaction	yield of **3b** (%)
1	Br	1:1:1:1	rt, o.n.[a]	28
2	Br	1:1:1:1	reflux, o.n.	37
3	Br	1:2:2:2	rt, o.n.	29
4	Br	1:3:1:1	rt, o.n.	61
5	Br	1:5:5:5	rt, o.n.	68
6	Br	1:5:5:0	reflux, o.n.	76
7	Br	1:5:5:5	reflux, o.n.	83
8	Br	1:10:10:10	rt, o.n.	58
9	Br	1:10:10:10	reflux, o.n.	88
10	Cl	1:5:5:5	reflux, o.n.	81

[a] o.n. = overnight.

The use of one molar ratio of **1b**, 1 or 2 molar ratio of **2b**, K_2CO_3, and TEA gave a low yield of **3b** (runs 1 and 3), and the yield of **3b** did not increase even under reflux (37%, run 2). Excess amounts (5 or 10 molar ratios) of **2a**, K_2CO_3, and TEA to benzylamine **1b** at room temperature gave **3b** in 68% and 58% yields (runs 5 and 8) and the yields increased to 83 and 88% under reflux (runs 7 and 9). In the absence of TEA as a base, the yield of **3b** was lower than that in run 7 (run 6). It suggested that the addition of a strong base increased the yield of **3b** in comparison between runs 6 and 7. The use of chloromethyloxirane **2b** instead of bromomethyloxirane **2a** gave almost the same yield of **3b** (81% yields in the case of **2b** (run 10) and 83% in the case of **2a** (run 7)). Thus, we were able to optimize the reaction conditions for oxazolidinones on the basis of our reaction mechanism. Pure product **3** was rationally identified on the basis of IR, NMR, elemental analysis, and mass spectra.

Several kinds of carbonate salts were examined to obtain **3** as shown in Table 3. Na_2CO_3, Cs_2CO_3, and Ag_2CO_3 (runs 2, 4, and 6) gave more than 75% yields of **3b**.

At the beginning of our study,[19] we examined various primary amines of propyl, isopropyl, *n*-butyl, heptyl, and cyclohexyl groups. When the reaction conditions of pri-

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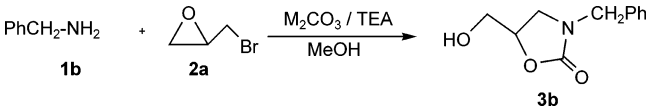
TABLE 3. The Yield of 3b Using Various Carbonate Salts



run[a]	M_2CO_3	molar ratio **1b/2a/** M_2CO_3/TEA	reaction	yield of **3b** (%)
1	K_2CO_3	1:5:5:5	reflux, under Ar, o.n.[b]	83
2	Na_2CO_3	1:5:5:5	reflux, under Ar, o.n.	77
3	Rb_2CO_3	1:5:5:5	reflux, under Ar, o.n.	28
4	Cs_2CO_3	1:5:5:5	reflux, under Ar, o.n.	82
5	Li_2CO_3	1:5:5:5	reflux, under Ar, o.n.	25
6	Ag_2CO_3	1:5:5:5	reflux, dark, under Ar, o.n.	75

[a] All reactions were carried out in MeOH. [b] o.n. = overnight.

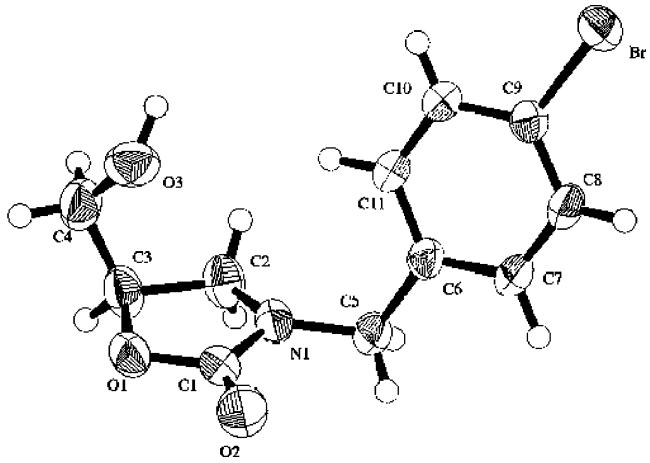
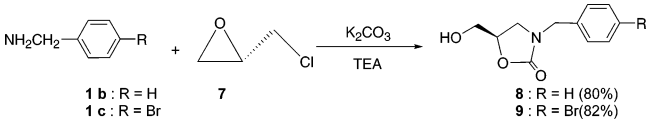


FIGURE 1.

SCHEME 4



mary amine **1** (2 equiv), bromomethyloxirane **2a** (2 equiv), and Ag_2CO_3 or K_2CO_3 (1 equiv) in methanol stirring overnight at room temperature were used, 36−50% yields of the corresponding oxazolidinones were obtained based on each amine. Application of similar optimum reaction conditions to benzylamine will give higher yield of oxazolidinones. The use of aniline as aromatic amine is now under study.

We also applied chiral halomethyloxirane to a synthesis for chiral oxazolidinones to confirm which route the reaction selected, I or II. The reactions of (*S*)-chloromethyloxirane (**7**) with benzylamine (**1b**) and *p*-bromobenzylamine (**1c**) under similar conditions to the above method to give oxazolidinones **8** and **9** were carried out (Scheme 4). The stereo structure of *N*-(*p*-bromobenzyl)-5-hydroxymethyloxazolidin-2-one (**9**) was confirmed by means of X-ray analysis (Figure 1).[20] In this reaction, the *S*-configuration of the oxirane ring inverted to the *R*-configuration at the 5-position of the oxazolidinone nucleus (Scheme 4). The results support route I in the reaction mechanism (Scheme 2) because route II will retain the *S*-configuration to give *S*-oxazolidinone in the use of *S*-chloromethyloxirane. Accordingly, the synthesis of oxazolidinone is supposed to proceed via route I.

In conclusion, the present synthetic method is characterized by a simple procedure, mild reaction conditions, high reaction yield, and high selectivity and will be useful to produce various kinds of *N*-substituted-5-hydroxymethyloxazolidin-2-one and chiral oxazolidinone. The five-membered ring compound, oxazolidinone, is more stable than the six-membered ring compound, oxazinanone.

Experimental Section

General Procedure for Oxazolidinone. Primary amine (1 mmol ratio) was added to methanol (5 mL) containing an excess amount of halomethyloxirane (5 or 10 mmol ratio), K_2CO_3 (5 or 10 mmol ratio), and TEA (5 or 10 mmol ratio) under reflux overnight. After the solution was cooled to room temperature, the reaction mixture was filtered for removing the solidified, unreacted carbonate salts. Then, the organic layer was evaporated and the residue was solved in AcOEt. The organic layer was washed with NaCl aq and dried using Na_2SO_4. The solvent was evaporated in vacuo. The residue was isolated by silica gel column chromatography with chloroform/methanol (10:1).

***N*-Benzyl-5-hydroxymethyloxazolidin-2-one (3b):** yield 88% as a pale yellow solid; mp 69−70 °C; IR (film) 3200−3620, 1730 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.32 (1H, dd, J = 6.5, 8.0 Hz), 3.44 (1H, dd, J = 8.0. 10.0 Hz), 3.62 (1H, dd, J = 13.0, 4.0 Hz), 3.85 (1H, dd, J = 13.0, 3.0 Hz), 4.38, 4.48 (d, 1H, J = 15.0 Hz), 4.58 (1H, m, J = 6.5, 10.0, 4.0, 3.0 Hz), 7.25−7.38 (5H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 45.1, 47.9, 62.6, 73.5, 127.7, 127.8, 128.6, 135.4, 156.2; MS (FAB) *m/z* 208 $(M + H)^+$. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.59; H, 6.32; N, 7.01.

***N*-Benzyl-5-hydroxyoxazinan-2-one (4b).** To a methanol (4 mL) solution of bromomethyloxirane **2a** (171 μL, 2.0 mmol) was added benzylamine (218 μL, 2.0 mmol). The reaction mixture was bubbled through CO_2 for 5 h and stirred overnight. The reaction mixture was evaporated in vacuo, and then the yellow residue was purified by silica gel column chromatography with chloroform/ethyl acetate (5:1) to give the pure product **4b** (163 mg, 39% unoptimized yield) as a pale yellow solid: mp 114−115 °C; IR (KBr) 3200−3620, 1678 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.17 (1H, ddd, J = 12.0, 3.0 Hz), 3.38 (1H, dd, J = 12.0, 4.0 Hz), 4.10 (1H, m), 4.20 (1H, dd, J = 3.0, 12.0 Hz), 4.23 (1H, dd, J = 2.5, 12.0 Hz), 4.43, 4.61 (1H, d, J = 15.0 Hz), 7.24−7.32 (5H, m); ^{13}C NMR (150 MHz, $CDCl_3$) δ 51.4, 52.7, 61.2, 70.5, 127.8, 128.1, 128.8, 136.2, 153.5; MS (EI) *m/z* 207 $(M)^+$. Anal. Calcd for $C_{11}H_{13}NO_3$: C, 63.76; H, 6.32; N, 6.76. Found: C, 63.62; H, 6.41; N, 6.66.

(*R*)-*N*-(*p*-Bromobenzyl)-5-hydroxymethyloxazolidin-2-one (9). *p*-Bromobenzylamine hydrochloride **1c** (100 mg, 0.45 mmol) was removed by washing with NaOH aq: yield 82% as prisms; mp 109−110 °C (crystallized from ethyl acetate); $[\alpha]^{21}_D$ = −12.5 (*c* 0.933, MeOH); IR (film) 3200−3620, 1729 cm^{-1}; ^1H NMR (600 MHz, $CDCl_3$) δ 3.32 (1H, dd, J = 7.0, 8.0 Hz), 3.40 (1H, dd, J = 8.0. 10.0 Hz), 3.57 (1H, dd, J = 12.0, 4.0 Hz), 3.83 (1H, dd, J = 12.0, 5.0 Hz), 4.32, 4.37 (1H, d, J = 15.0 Hz), 4.55 (1H, dt, J = 10.0, 7.0, 5.0, 4.0 Hz), 7.13, 7.45 (1H, d, J = 8.0 Hz); ^{13}C NMR (150 MHz, $CDCl_3$) δ 45.0, 47.7, 62.9, 73.5, 121.9, 129.7, 131.9, 134.6, 157.9; MS (FAB) *m/z* 285, 287 $(M)^+$. Anal. Calcd for $C_{11}H_{12}NO_3Br$: C, 46.18; H, 4.23; N, 4.90. Found: C, 46.16; H, 4.28; N, 5.09.

Supporting Information Available: Experimental details. This material is available free of charge via the Internet at http://pubs.acs.org.

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(20) X-ray data was deposited in the Cambridge Crystallographic Data Centre in CIF format as CCDC 269747 for **9**.